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(54) Title: NON-ENDOGENOUS, CONSTITUTIVELY ACTIVATED HUMAN G PROTEIN-COUPLED RECEPTORS

## (57) Abstract

The invention disclosed in this patent document relates to transmembrane receptors, more particularly to a human G protein-coupled receptor for which the endogenous ligand is unknown ("orphan GPCR receptors"), and most particularly to mutated (non-endogenous) versions of the human GPCRs for evidence of constitutive activity.

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**NON-ENDOGENOUS, CONSTITUTIVELY ACTIVATED  
HUMAN G PROTEIN-COUPLED RECEPTORS**

This patent application is a continuation-in-part of, and claims priority from, U.S. Serial Number 09/170,496, filed with the United States Patent and Trademark Office on  
5 October 13, 1998. This application also claims the benefit of priority from the following provisional applications, all filed via U.S. Express Mail with the United States Patent and Trademark Office on the indicated dates: U.S. Provisional Number 60/110,060, filed November 27, 1998; U.S. Provisional Number 60/120,416, filed February 16, 1999; U.S. Provisional Number 60/121,852, filed February 26, 1999 claiming benefit of U.S.  
10 Provisional Number 60/109,213, filed November 20, 1998; U.S. Provisional Number 60/123,944, filed March 12, 1999; U.S. Provisional Number 60/123,945, filed March 12, 1999; U.S. Provisional Number 60/123,948, filed March 12, 1999; U.S. Provisional Number 60/123,951, filed March 12, 1999; U.S. Provisional Number 60/123,946, filed March 12, 1999; U.S. Provisional Number 60/123,949, filed March 12, 1999; U.S.  
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## FIELD OF THE INVENTION

The invention disclosed in this patent document relates to transmembrane receptors, and more particularly to human G protein-coupled receptors, and specifically to

GPCRs that have been altered to establish or enhance constitutive activity of the receptor. Preferably, the altered GPCRs are used for the direct identification of candidate compounds as receptor agonists, inverse agonists or partial agonists having potential applicability as therapeutic agents.

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## BACKGROUND OF THE INVENTION

Although a number of receptor classes exist in humans, by far the most abundant and therapeutically relevant is represented by the G protein-coupled receptor (GPCR or GPCRs) class. It is estimated that there are some 100,000 genes within the human genome, and of these, approximately 2%, or 2,000 genes, are estimated to code for GPCRs. Receptors, including GPCRs, for which the endogenous ligand has been identified are referred to as "known" receptors, while receptors for which the endogenous ligand has not been identified are referred to as "orphan" receptors. GPCRs represent an important area for the development of pharmaceutical products: from approximately 20 of the 100 known GPCRs, 60% of all prescription pharmaceuticals have been developed.

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GPCRs share a common structural motif. All these receptors have seven sequences of between 22 to 24 hydrophobic amino acids that form seven alpha helices, each of which spans the membrane (each span is identified by number, *i.e.*, transmembrane-1 (TM-1), transmebrane-2 (TM-2), etc.). The transmembrane helices are joined by strands of amino acids between transmembrane-2 and transmembrane-3, transmembrane-4 and transmembrane-5, and transmembrane-6 and transmembrane-7 on the exterior, or "extracellular" side, of the cell membrane (these are referred to as "extracellular" regions 1, 2 and 3 (EC-1, EC-2 and EC-3), respectively). The transmembrane helices are also joined by strands of amino acids between transmembrane-1 and transmembrane-2, transmembrane-3 and transmembrane-4, and

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transmembrane-5 and transmembrane-6 on the interior, or "intracellular" side, of the cell membrane (these are referred to as "intracellular" regions 1, 2 and 3 (IC-1, IC-2 and IC-3), respectively). The "carboxy" ("C") terminus of the receptor lies in the intracellular space within the cell, and the "amino" ("N") terminus of the receptor lies in the extracellular space outside of the cell.

Generally, when an endogenous ligand binds with the receptor (often referred to as "activation" of the receptor), there is a change in the conformation of the intracellular region that allows for coupling between the intracellular region and an intracellular "G-protein." It has been reported that GPCRs are "promiscuous" with respect to G proteins, *i.e.*, that a GPCR can interact with more than one G protein. *See*, Kenakin, T., 43 *Life Sciences* 1095 (1988). Although other G proteins exist, currently, Gq, Gs, Gi, Gz and Go are G proteins that have been identified. Endogenous ligand-activated GPCR coupling with the G-protein begins a signaling cascade process (referred to as "signal transduction"). Under normal conditions, signal transduction ultimately results in cellular activation or cellular inhibition. It is thought that the IC-3 loop as well as the carboxy terminus of the receptor interact with the G protein.

Under physiological conditions, GPCRs exist in the cell membrane in equilibrium between two different conformations: an "inactive" state and an "active" state. A receptor in an inactive state is unable to link to the intracellular signaling transduction pathway to produce a biological response. Changing the receptor conformation to the active state allows linkage to the transduction pathway (via the G-protein) and produces a biological response.

A receptor may be stabilized in an active state by an endogenous ligand or a

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compound such as a drug. Recent discoveries, including but not exclusively limited to modifications to the amino acid sequence of the receptor, provide means other than endogenous ligands or drugs to promote and stabilize the receptor in the active state conformation. These means effectively stabilize the receptor in an active state by  
5 simulating the effect of an endogenous ligand binding to the receptor. Stabilization by such ligand-independent means is termed "constitutive receptor activation."

### SUMMARY OF THE INVENTION

Disclosed herein are non-endogenous versions of endogenous, human GPCRs and uses thereof.

10

### BRIEF DESCRIPTION OF THE DRAWINGS

**Figure 1** is a representation of 8XCRES-Luc reporter plasmid (*see*, Example 4(c)3.)

**Figures 2A and 2B** are graphic representations of the results of ATP and ADP binding to endogenous TDAG8 (2A) and comparisons in serum and serum free media (2B).

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**Figure 3** is a graphic representation of the comparative signaling results of CMV versus the GPCR Fusion Protein H9(F236K):Gsa.

### DETAILED DESCRIPTION

The scientific literature that has evolved around receptors has adopted a number of terms to refer to ligands having various effects on receptors. For clarity and  
20 consistency, the following definitions will be used throughout this patent document. To the extent that these definitions conflict with other definitions for these terms, the following definitions shall control:

**AGONISTS** shall mean materials (*e.g.*, ligands, candidate compounds) that

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activate the intracellular response when they bind to the receptor, or enhance GTP binding to membranes.

AMINO ACID ABBREVIATIONS used herein are set out in Table A:

TABLE A			
5	ALANINE	ALA	A
	ARGININE	ARG	R
	ASPARAGINE	ASN	N
	ASPARTIC ACID	ASP	D
	CYSTEINE	CYS	C
10	GLUTAMIC ACID	GLU	E
	GLUTAMINE	GLN	Q
	GLYCINE	GLY	G
	HISTIDINE	HIS	H
	ISOLEUCINE	ILE	I
15	LEUCINE	LEU	L
	LYSINE	LYS	K
	METHIONINE	MET	M
	PHENYLALANINE	PHE	F
	PROLINE	PRO	P
20	SERINE	SER	S
	THREONINE	THR	T
	TRYPTOPHAN	TRP	W
	TYROSINE	TYR	Y
	VALINE	VAL	V

25 **PARTIAL AGONISTS** shall mean materials (*e.g.*, ligands, candidate compounds) that activate the intracellular response when they bind to the receptor to a lesser degree/extent than do agonists, or enhance GTP binding to membranes to a lesser degree/extent than do agonists.

**ANTAGONIST** shall mean materials (*e.g.*, ligands, candidate compounds) that  
 30 competitively bind to the receptor at the same site as the agonists but which do not activate the intracellular response initiated by the active form of the receptor, and can thereby inhibit the intracellular responses by agonists or partial agonists. **ANTAGONISTS** do not diminish the baseline intracellular response in the absence of an agonist or partial agonist.

**CANDIDATE COMPOUND** shall mean a molecule (for example, and not limitation,



a chemical compound) that is amenable to a screening technique. Preferably, the phrase "candidate compound" does not include compounds which were publicly known to be compounds selected from the group consisting of inverse agonist, agonist or antagonist to a receptor, as previously determined by an indirect identification process ("indirectly identified  
5 compound"); more preferably, not including an indirectly identified compound which has previously been determined to have therapeutic efficacy in at least one mammal; and, most preferably, not including an indirectly identified compound which has previously been determined to have therapeutic utility in humans.

**COMPOSITION** means a material comprising at least one component; a  
10 "pharmaceutical composition" is an example of a composition.

**COMPOUND EFFICACY** shall mean a measurement of the ability of a compound to inhibit or stimulate receptor functionality, as opposed to receptor binding affinity. Exemplary means of detecting compound efficacy are disclosed in the Example section of this patent document.

15 **CODON** shall mean a grouping of three nucleotides (or equivalents to nucleotides) which generally comprise a nucleoside (adenosine (A), guanosine (G), cytidine (C), uridine (U) and thymidine (T)) coupled to a phosphate group and which, when translated, encodes an amino acid.

**CONSTITUTIVELY ACTIVATED RECEPTOR** shall mean a receptor subject to  
20 constitutive receptor activation. A constitutively activated receptor can be endogenous or non-endogenous.

**CONSTITUTIVE RECEPTOR ACTIVATION** shall mean stabilization of a receptor in the active state by means other than binding of the receptor with its endogenous

ligand or a chemical equivalent thereof.

**CONTACT** or **CONTACTING** shall mean bringing at least two moieties together, whether in an in vitro system or an in vivo system.

**DIRECTLY IDENTIFYING** or **DIRECTLY IDENTIFIED**, in relationship to the  
5 phrase "candidate compound", shall mean the screening of a candidate compound against a constitutively activated receptor, preferably a constitutively activated orphan receptor, and most preferably against a constitutively activated G protein-coupled cell surface orphan receptor, and assessing the compound efficacy of such compound. This phrase is, under no  
10 circumstances, to be interpreted or understood to be encompassed by or to encompass the phrase "indirectly identifying" or "indirectly identified."

**ENDOGENOUS** shall mean a material that a mammal naturally produces. **ENDOGENOUS** in reference to, for example and not limitation, the term "receptor," shall mean that which is naturally produced by a mammal (for example, and not limitation, a human) or a virus. By contrast, the term **NON-ENDOGENOUS** in this context shall mean  
15 that which is not naturally produced by a mammal (for example, and not limitation, a human) or a virus. For example, and not limitation, a receptor which is not constitutively active in its endogenous form, but when manipulated becomes constitutively active, is most preferably referred to herein as a "non-endogenous, constitutively activated receptor." Both terms can be utilized to describe both "in vivo" and "in vitro" systems. For example, and not limitation,  
20 in a screening approach, the endogenous or non-endogenous receptor may be in reference to an in vitro screening system. As a further example and not limitation, where the genome of a mammal has been manipulated to include a non-endogenous constitutively activated receptor, screening of a candidate compound by means of an in vivo system is viable.

**G PROTEIN COUPLED RECEPTOR FUSION PROTEIN and GPCR FUSION**

**PROTEIN**, in the context of the invention disclosed herein, each mean a non-endogenous protein comprising an endogenous, constitutively activate GPCR or a non-endogenous, constitutively activated GPCR fused to at least one G protein, most preferably the alpha ( $\alpha$ ) subunit of such G protein (this being the subunit that binds GTP), with the G protein preferably being of the same type as the G protein that naturally couples with endogenous orphan GPCR. For example, and not limitation, in an endogenous state, if the G protein "G $\alpha$ " is the predominate G protein that couples with the GPCR, a GPCR Fusion Protein based upon the specific GPCR would be a non-endogenous protein comprising the GPCR fused to G $\alpha$ ; in some circumstances, as will be set forth below, a non-predominant G protein can be fused to the GPCR. The G protein can be fused directly to the c-terminus of the constitutively active GPCR or there may be spacers between the two.

**HOST CELL** shall mean a cell capable of having a Plasmid and/or Vector incorporated therein. In the case of a prokaryotic Host Cell, a Plasmid is typically replicated as a autonomous molecule as the Host Cell replicates (generally, the Plasmid is thereafter isolated for introduction into a eukaryotic Host Cell); in the case of a eukaryotic Host Cell, a Plasmid is integrated into the cellular DNA of the Host Cell such that when the eukaryotic Host Cell replicates, the Plasmid replicates. Preferably, for the purposes of the invention disclosed herein, the Host Cell is eukaryotic, more preferably, mammalian, and most preferably selected from the group consisting of 293, 293T and COS-7 cells.

**INDIRECTLY IDENTIFYING** or **INDIRECTLY IDENTIFIED** means the traditional approach to the drug discovery process involving identification of an endogenous ligand specific for an endogenous receptor, screening of candidate compounds against the

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receptor for determination of those which interfere and/or compete with the ligand-receptor interaction, and assessing the efficacy of the compound for affecting at least one second messenger pathway associated with the activated receptor.

**INHIBIT** or **INHIBITING**, in relationship to the term "response" shall mean that a  
5 response is decreased or prevented in the presence of a compound as opposed to in the absence of the compound.

**INVERSE AGONISTS** shall mean materials (*e.g.*, ligand, candidate compound) which bind to either the endogenous form of the receptor or to the constitutively activated form of the receptor, and which inhibit the baseline intracellular response initiated by the  
10 active form of the receptor below the normal base level of activity which is observed in the absence of agonists or partial agonists, or decrease GTP binding to membranes. Preferably, the baseline intracellular response is inhibited in the presence of the inverse agonist by at least 30%, more preferably by at least 50%, and most preferably by at least 75%, as compared with the baseline response in the absence of the inverse agonist.

15 **KNOWN RECEPTOR** shall mean an endogenous receptor for which the endogenous ligand specific for that receptor has been identified.

**LIGAND** shall mean an endogenous, naturally occurring molecule specific for an endogenous, naturally occurring receptor.

**MUTANT** or **MUTATION** in reference to an endogenous receptor's nucleic acid  
20 and/or amino acid sequence shall mean a specified change or changes to such endogenous sequences such that a mutated form of an endogenous, non-constitutively activated receptor evidences constitutive activation of the receptor. In terms of equivalents to specific sequences, a subsequent mutated form of a human receptor is considered to be equivalent to

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a first mutation of the human receptor if (a) the level of constitutive activation of the subsequent mutated form of a human receptor is substantially the same as that evidenced by the first mutation of the receptor; and (b) the percent sequence (amino acid and/or nucleic acid) homology between the subsequent mutated form of the receptor and the first mutation  
5 of the receptor is at least about 80%, more preferably at least about 90% and most preferably at least 95%. Ideally, and owing to the fact that the most preferred cassettes disclosed herein for achieving constitutive activation includes a single amino acid and/or codon change between the endogenous and the non-endogenous forms of the GPCR, the percent sequence homology should be at least 98%.

10       **NON-ORPHAN RECEPTOR** shall mean an endogenous naturally occurring molecule specific for an endogenous naturally occurring ligand wherein the binding of a ligand to a receptor activates an intracellular signaling pathway.

**ORPHAN RECEPTOR** shall mean an endogenous receptor for which the endogenous ligand specific for that receptor has not been identified or is not known.

15       **PHARMACEUTICAL COMPOSITION** shall mean a composition comprising at least one active ingredient, whereby the composition is amenable to investigation for a specified, efficacious outcome in a mammal (for example, and not limitation, a human). Those of ordinary skill in the art will understand and appreciate the techniques appropriate for determining whether an active ingredient has a desired efficacious outcome based upon the  
20 needs of the artisan.

**PLASMID** shall mean the combination of a Vector and cDNA. Generally, a Plasmid is introduced into a Host Cell for the purposes of replication and/or expression of the cDNA as a protein.

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**STIMULATE** or **STIMULATING**, in relationship to the term "response" shall mean that a response is increased in the presence of a compound as opposed to in the absence of the compound.

**VECTOR** in reference to cDNA shall mean a circular DNA capable of incorporating  
5 at least one cDNA and capable of incorporation into a Host Cell.

The order of the following sections is set forth for presentational efficiency and is not intended, nor should be construed, as a limitation on the disclosure or the claims to follow.

**A. Introduction**

The traditional study of receptors has always proceeded from the a priori assumption  
10 (historically based) that the endogenous ligand must first be identified before discovery could proceed to find antagonists and other molecules that could affect the receptor. Even in cases where an antagonist might have been known first, the search immediately extended to looking for the endogenous ligand. This mode of thinking has persisted in receptor research even after the discovery of constitutively activated receptors. What has not been heretofore recognized  
15 is that it is the active state of the receptor that is most useful for discovering agonists, partial agonists, and inverse agonists of the receptor. For those diseases which result from an overly active receptor or an under-active receptor, what is desired in a therapeutic drug is a compound which acts to diminish the active state of a receptor or enhance the activity of the receptor, respectively, not necessarily a drug which is an antagonist to the endogenous ligand.  
20 This is because a compound that reduces or enhances the activity of the active receptor state need not bind at the same site as the endogenous ligand. Thus, as taught by a method of this invention, any search for therapeutic compounds should start by screening compounds against the ligand-independent active state.

**B. Identification of Human GPCRs**

The efforts of the Human Genome project has led to the identification of a plethora of information regarding nucleic acid sequences located within the human genome; it has been the case in this endeavor that genetic sequence information has been made available without an understanding or recognition as to whether or not any particular genomic sequence does or may contain open-reading frame information that translate human proteins. Several methods of identifying nucleic acid sequences within the human genome are within the purview of those having ordinary skill in the art. For example, and not limitation, a variety of human GPCRs, disclosed herein, were discovered by reviewing the GenBank™ database, while other GPCRs were discovered by utilizing a nucleic acid sequence of a GPCR, previously sequenced, to conduct a BLAST™ search of the EST database. Table B, below, lists several endogenous GPCRs that we have discovered, along with a GPCR's respective homologous receptor.

**TABLE B**

	Disclosed Human Orphan GPCRs	Accession Number Identified	Open Reading Frame (Base Pairs)	Per Cent Homology To Designated GPCR	Reference To Homologous GPCR (Accession No.)
15	<b>hARE-3</b>	AL033379	1,260 bp	52.3% LPA-R	U92642
20	<b>hARE-4</b>	AC006087	1,119 bp	36% P2Y5	AF000546
	<b>hARE-5</b>	AC006255	1,104 bp	32% <i>Oryzias latipes</i>	D43633
	<b>hGPR27</b>	AA775870	1,128 bp		
	<b>hARE-1</b>	AI090920	999 bp	43% KIAA0001	D13626
	<b>hARE-2</b>	AA359504	1,122 bp	53% GPR27	
25	<b>hPPR1</b>	H67224	1,053 bp	39% EBI1	L31581
	<b>hG2A</b>	AA754702	1,113 bp	31% GPR4	L36148

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	<b>hRUP3</b>	AL035423	1,005 bp	30%	2133653
				<i>Drosophila</i>	
				<i>melanogaster</i>	
	<b>hRUP4</b>	AI307658	1,296 bp	32% pNPGPR	NP_004876
				28% and 29 %	AAC41276
				<i>Zebra fish</i> Ya	and
				and Yb,	AAB94616
				respectively	
	<b>hRUP5</b>	AC005849	1,413 bp	25% DEZ	Q99788
				23% FMLPR	P21462
	<b>hRUP6</b>	AC005871	1,245 bp	48% GPR66	NP_006047
5	<b>hRUP7</b>	AC007922	1,173 bp	43% H3R	AF140538
	<b>hCHN3</b>	EST 36581	1,113 bp	53% GPR27	
	<b>hCHN4</b>	AA804531	1,077 bp	32% thrombin	4503637
	<b>hCHN6</b>	EST 2134670	1,503 bp	36% edg-1	NP_001391
	<b>hCHN8</b>	EST 764455	1,029 bp	47%	D13626
				KIAA0001	
10	<b>hCHN9</b>	EST 1541536	1,077 bp	41% LTB4R	NM_000752
	<b>hCHN10</b>	EST 1365839	1,055 bp	35% P2Y	NM_002563

Receptor homology is useful in terms of gaining an appreciation of a role of the receptors within the human body. As the patent document progresses, we will disclose techniques for mutating these receptors to establish non-endogenous, constitutively activated versions of these receptors.

The techniques disclosed herein have also been applied to other human, orphan GPCRs known to the art, as will be apparent as the patent document progresses.

### C. Receptor Screening

Screening candidate compounds against a non-endogenous, constitutively activated version of the human GPCRs disclosed herein allows for the direct identification of candidate compounds which act at this cell surface receptor, without requiring use of the receptor's endogenous ligand. By determining areas within the body where the endogenous version of human GPCRs disclosed herein is expressed and/or over-expressed, it is possible to determine related disease/disorder states which are associated with the expression and/or over-expression



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of the receptor; such an approach is disclosed in this patent document.

With respect to creation of a mutation that may evidence constitutive activation of the human GPCR disclosed herein is based upon the distance from the proline residue at which is presumed to be located within TM6 of the GPCR; this algorithmic technique is disclosed  
5 in co-pending and commonly assigned patent document U.S. Serial Number 09/170,496, incorporated herein by reference. The algorithmic technique is not predicated upon traditional sequence "alignment" but rather a specified distance from the aforementioned TM6 proline residue. By mutating the amino acid residue located 16 amino acid residues from this residue (presumably located in the IC3 region of the receptor) to, most preferably, a lysine residue,  
10 such activation may be obtained. Other amino acid residues may be useful in the mutation at this position to achieve this objective.

#### **D. Disease/Disorder Identification and/or Selection**

As will be set forth in greater detail below, most preferably inverse agonists to the non-endogenous, constitutively activated GPCR can be identified by the methodologies of this  
15 invention. Such inverse agonists are ideal candidates as lead compounds in drug discovery programs for treating diseases related to this receptor. Because of the ability to directly identify inverse agonists to the GPCR, thereby allowing for the development of pharmaceutical compositions, a search for diseases and disorders associated with the GPCR is relevant. For example, scanning both diseased and normal tissue samples for the presence  
20 of the GPCR now becomes more than an academic exercise or one which might be pursued along the path of identifying an endogenous ligand to the specific GPCR. Tissue scans can be conducted across a broad range of healthy and diseased tissues. Such tissue scans provide a preferred first step in associating a specific receptor with a disease and/or disorder. *See, for*

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*example*, co-pending application (docket number ARE-0050) for exemplary dot-blot and RT-PCR results of several of the GPCRs disclosed herein.

Preferably, the DNA sequence of the human GPCR is used to make a probe for (a) dot-blot analysis against tissue-mRNA, and/or (b) RT-PCR identification of the expression  
5 of the receptor in tissue samples. The presence of a receptor in a tissue source, or a diseased tissue, or the presence of the receptor at elevated concentrations in diseased tissue compared to a normal tissue, can be preferably utilized to identify a correlation with a treatment regimen, including but not limited to, a disease associated with that disease. Receptors can equally well be localized to regions of organs by this technique. Based on  
10 the known functions of the specific tissues to which the receptor is localized, the putative functional role of the receptor can be deduced.

#### **E. Screening of Candidate Compounds**

##### **1. Generic GPCR screening assay techniques**

When a G protein receptor becomes constitutively active, it binds to a G protein (*e.g.*,  
15 Gq, Gs, Gi, Gz, Go) and stimulates the binding of GTP to the G protein. The G protein then acts as a GTPase and slowly hydrolyzes the GTP to GDP, whereby the receptor, under normal conditions, becomes deactivated. However, constitutively activated receptors continue to exchange GDP to GTP. A non-hydrolyzable analog of GTP, [<sup>35</sup>S]GTPγS, can be used to monitor enhanced binding to membranes which express constitutively activated receptors.  
20 It is reported that [<sup>35</sup>S]GTPγS can be used to monitor G protein coupling to membranes in the absence and presence of ligand. An example of this monitoring, among other examples well-known and available to those in the art, was reported by Traynor and Nahorski in 1995. The preferred use of this assay system is for initial screening of candidate compounds because the

system is generically applicable to all G protein-coupled receptors regardless of the particular G protein that interacts with the intracellular domain of the receptor.

## 2. Specific GPCR screening assay techniques

Once candidate compounds are identified using the "generic" G protein-coupled  
5 receptor assay (*i.e.*, an assay to select compounds that are agonists, partial agonists, or inverse agonists), further screening to confirm that the compounds have interacted at the receptor site is preferred. For example, a compound identified by the "generic" assay may not bind to the receptor, but may instead merely "uncouple" the G protein from the intracellular domain.

### a. Gs, Gz and Gi.

10 Gs stimulates the enzyme adenylyl cyclase. Gi (and Gz and Go), on the other hand, inhibit this enzyme. Adenylyl cyclase catalyzes the conversion of ATP to cAMP; thus, constitutively activated GPCRs that couple the Gs protein are associated with increased cellular levels of cAMP. On the other hand, constitutively activated GPCRs that couple Gi (or Gz, Go) protein are associated with decreased cellular levels of cAMP. *See, generally,*  
15 "Indirect Mechanisms of Synaptic Transmission," Chpt. 8, From Neuron To Brain (3<sup>rd</sup> Ed.) Nichols, J.G. et al eds. Sinauer Associates, Inc. (1992). Thus, assays that detect cAMP can be utilized to determine if a candidate compound is, *e.g.*, an inverse agonist to the receptor (*i.e.*, such a compound would decrease the levels of cAMP). A variety of approaches known in the art for measuring cAMP can be utilized; a most preferred approach relies upon the use  
20 of anti-cAMP antibodies in an ELISA-based format. Another type of assay that can be utilized is a whole cell second messenger reporter system assay. Promoters on genes drive the expression of the proteins that a particular gene encodes. Cyclic AMP drives gene expression by promoting the binding of a cAMP-responsive DNA binding protein or

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transcription factor (CREB) that then binds to the promoter at specific sites called cAMP response elements and drives the expression of the gene. Reporter systems can be constructed which have a promoter containing multiple cAMP response elements before the reporter gene, *e.g.*,  $\beta$ -galactosidase or luciferase. Thus, a constitutively activated Gs-linked receptor causes the accumulation of cAMP that then activates the gene and expression of the reporter protein. The reporter protein such as  $\beta$ -galactosidase or luciferase can then be detected using standard biochemical assays (Chen et al. 1995).

*b. Go and Gq.*

Gq and Go are associated with activation of the enzyme phospholipase C, which in turn hydrolyzes the phospholipid  $\text{PIP}_2$ , releasing two intracellular messengers: diacylglycerol (DAG) and inositol 1,4,5-trisphosphate ( $\text{IP}_3$ ). Increased accumulation of  $\text{IP}_3$  is associated with activation of Gq- and Go-associated receptors. *See, generally*, "Indirect Mechanisms of Synaptic Transmission," Chpt. 8, From Neuron To Brain (3<sup>rd</sup> Ed.) Nichols, J.G. et al eds. Sinauer Associates, Inc. (1992). Assays that detect  $\text{IP}_3$  accumulation can be utilized to determine if a candidate compound is, *e.g.*, an inverse agonist to a Gq- or Go-associated receptor (*i.e.*, such a compound would decrease the levels of  $\text{IP}_3$ ). Gq-associated receptors can also be examined using an AP1 reporter assay in that Gq-dependent phospholipase C causes activation of genes containing AP1 elements; thus, activated Gq-associated receptors will evidence an increase in the expression of such genes, whereby inverse agonists thereto will evidence a decrease in such expression, and agonists will evidence an increase in such expression. Commercially available assays for such detection are available.

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### 3. GPCR Fusion Protein

The use of an endogenous, constitutively activate orphan GPCR or a non-endogenous, constitutively activated orphan GPCR, for use in screening of candidate compounds for the direct identification of inverse agonists, agonists and partial agonists provide an interesting  
5 screening challenge in that, by definition, the receptor is active even in the absence of an endogenous ligand bound thereto. Thus, in order to differentiate between, *e.g.*, the non-endogenous receptor in the presence of a candidate compound and the non-endogenous receptor in the absence of that compound, with an aim of such a differentiation to allow for an understanding as to whether such compound may be an inverse agonist, agonist, partial  
10 agonist or have no affect on such a receptor, it is preferred that an approach be utilized that can enhance such differentiation. A preferred approach is the use of a GPCR Fusion Protein.

Generally, once it is determined that a non-endogenous orphan GPCR has been constitutively activated using the assay techniques set forth above (as well as others), it is possible to determine the predominant G protein that couples with the endogenous GPCR.  
15 Coupling of the G protein to the GPCR provides a signaling pathway that can be assessed. Because it is most preferred that screening take place by use of a mammalian expression system, such a system will be expected to have endogenous G protein therein. Thus, by definition, in such a system, the non-endogenous, constitutively activated orphan GPCR will continuously signal. In this regard, it is preferred that this signal be enhanced such that in the  
20 presence of, *e.g.*, an inverse agonist to the receptor, it is more likely that it will be able to more readily differentiate, particularly in the context of screening, between the receptor when it is contacted with the inverse agonist.

The GPCR Fusion Protein is intended to enhance the efficacy of G protein coupling

with the non-endogenous GPCR. The GPCR Fusion Protein is preferred for screening with a non-endogenous, constitutively activated GPCR because such an approach increases the signal that is most preferably utilized in such screening techniques. This is important in facilitating a significant "signal to noise" ratio; such a significant ratio is import preferred for  
5 the screening of candidate compounds as disclosed herein.

The construction of a construct useful for expression of a GPCR Fusion Protein is within the purview of those having ordinary skill in the art. Commercially available expression vectors and systems offer a variety of approaches that can fit the particular needs of an investigator. The criteria of importance for such a GPCR Fusion Protein construct is  
10 that the endogenous GPCR sequence and the G protein sequence both be in-frame (preferably, the sequence for the endogenous GPCR is upstream of the G protein sequence) and that the "stop" codon of the GPCR must be deleted or replaced such that upon expression of the GPCR, the G protein can also be expressed. The GPCR can be linked directly to the G protein, or there can be spacer residues between the two (preferably, no more than about 12,  
15 although this number can be readily ascertained by one of ordinary skill in the art). We have a preference (based upon convenience) of use of a spacer in that some restriction sites that are not used will, effectively, upon expression, become a spacer. Most preferably, the G protein that couples to the non-endogenous GPCR will have been identified prior to the creation of the GPCR Fusion Protein construct. Because there are only a few G proteins that have been  
20 identified, it is preferred that a construct comprising the sequence of the G protein (*i.e.*, a universal G protein construct) be available for insertion of an endogenous GPCR sequence therein; this provides for efficiency in the context of large-scale screening of a variety of different endogenous GPCRs having different sequences.

As noted above, constitutively activated GPCRs that couple to Gi, Gz and Go are expected to inhibit the formation of cAMP making assays based upon these types of GPCRs challenging (*i.e.*, the cAMP signal decreases upon activation thus making the direct identification of, *e.g.*, inverse agonists (which would further decrease this signal), interesting).

- 5 As will be disclosed herein, we have ascertained that for these types of receptors, it is possible to create a GPCR Fusion Protein that is not based upon the endogenous GPCR's endogenous G protein, in an effort to establish a viable cyclase-based assay. Thus, for example, a Gz coupled receptor such as H9, a GPCR Fusion Protein can be established that utilizes a Gs fusion protein - we believe that such a fusion construct, upon expression, "drives" or "forces"
- 10 the non-endogenous GPCR to couple with, *e.g.*, Gs rather than the "natural" Gz protein, such that a cyclase-based assay can be established. Thus, for Gi, Gz and Go coupled receptors, we prefer that that when a GPCR Fusion Protein is used and the assay is based upon detection of adenylyl cyclase activity, that the fusion construct be established with Gs (or an equivalent G protein that stimulates the formation of the enzyme adenylyl cyclase).

15 **F. Medicinal Chemistry**

- Generally, but not always, direct identification of candidate compounds is preferably conducted in conjunction with compounds generated via combinatorial chemistry techniques, whereby thousands of compounds are randomly prepared for such analysis. Generally, the results of such screening will be compounds having unique core structures; thereafter, these
- 20 compounds are preferably subjected to additional chemical modification around a preferred core structure(s) to further enhance the medicinal properties thereof. Such techniques are known to those in the art and will not be addressed in detail in this patent document.

### G. Pharmaceutical compositions

Candidate compounds selected for further development can be formulated into pharmaceutical compositions using techniques well known to those in the art. Suitable pharmaceutically-acceptable carriers are available to those in the art; for example, see  
5 Remington's Pharmaceutical Sciences, 16<sup>th</sup> Edition, 1980, Mack Publishing Co., (Oslo et al., eds.)

### H. Other Utility

Although a preferred use of the non-endogenous versions the human GPCRs disclosed herein may be for the direct identification of candidate compounds as inverse agonists,  
10 agonists or partial agonists (preferably for use as pharmaceutical agents), these versions of human GPCRs can also be utilized in research settings. For example, *in vitro* and *in vivo* systems incorporating GPCRs can be utilized to further elucidate and understand the roles these receptors play in the human condition, both normal and diseased, as well as understanding the role of constitutive activation as it applies to understanding the signaling  
15 cascade. The value in non-endogenous human GPCRs is that their utility as a research tool is enhanced in that, because of their unique features, non-endogenous human GPCRs can be used to understand the role of these receptors in the human body before the endogenous ligand therefor is identified. Other uses of the disclosed receptors will become apparent to those in the art based upon, *inter alia*, a review of this patent document.

20

### EXAMPLES

The following examples are presented for purposes of elucidation, and not limitation, of the present invention. While specific nucleic acid and amino acid sequences are disclosed herein, those of ordinary skill in the art are credited with the ability to make minor



modifications to these sequences while achieving the same or substantially similar results reported below. The traditional approach to application or understanding of sequence cassettes from one sequence to another (e.g. from rat receptor to human receptor or from human receptor A to human receptor B) is generally predicated upon sequence alignment techniques whereby the sequences are aligned in an effort to determine areas of commonality. The mutational approach disclosed herein does not rely upon this approach but is instead based upon an algorithmic approach and a positional distance from a conserved proline residue located within the TM6 region of human GPCRs. Once this approach is secured, those in the art are credited with the ability to make minor modifications thereto to achieve substantially the same results (*i.e.*, constitutive activation) disclosed herein. Such modified approaches are considered within the purview of this disclosure

**Example 1**  
**ENDOGENOUS HUMAN GPCRS**

**1. Identification of Human GPCRs**

Certain of the disclosed endogenous human GPCRs were identified based upon a review of the GenBank™ database information. While searching the database, the following cDNA clones were identified as evidenced below (Table C).

**TABLE C**

Disclosed Human Orphan GPCRs	Accession Number	Complete DNA Sequence (Base Pairs)	Open Reading Frame (Base Pairs)	Nucleic Acid SEQ.ID. NO.	Amino Acid SEQ.ID. NO.
hARE-3	AL033379	111,389 bp	1,260 bp	1	2
hARE-4	AC006087	226,925 bp	1,119 bp	3	4
hARE-5	AC006255	127,605 bp	1,104 bp	5	6
hRUP3	AL035423	140,094 bp	1,005 bp	7	8

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hRUP5	AC005849	169,144 bp	1,413 bp	9	10
hRUP6	AC005871	218,807 bp	1,245 bp	11	12
hRUP7	AC007922	158,858 bp	1,173 bp	13	14

Other disclosed endogenous human GPCRs were identified by conducting a BLAST™ search of EST database (dbest) using the following EST clones as query sequences. The following EST clones identified were then used as a probe to screen a human genomic library (Table D).

TABLE D

	Disclosed Human Orphan GPCRs	Query (Sequence)	EST Clone/ Accession No. Identified	Open Reading Frame (Base Pairs)	Nucleic Acid SEQ.ID.NO.	Amino Acid SEQ.ID.NO.
10	hGPCR27	Mouse GPCR27	AA775870	1,125 bp	17	18
	hARE-1	TDAG	1689643	999 bp	19	20
			AI090920			
15	hARE-2	GPCR27	68530	1,122 bp	21	22
			AA359504			
	hPPR1	Bovine PPR1	238667	1,053 bp	23	24
			H67224			
	hG2A	Mouse 1179426	See Example 2(a), below	1,113 bp	25	26
	hCHN3	N.A.	EST 36581 (full length)	1,113 bp	27	28
	hCHN4	TDAG	1184934	1,077 bp	29	30
			AA804531			
20	hCHN6	N.A.	EST 2134670 (full length)	1,503 bp	31	32
	hCHN8	KIAA0001	EST 764455	1,029 bp	33	34
	hCHN 9	1365839	EST 1541536	1,077 bp	35	36
	hCHN10	Mouse EST 1365839	Human 1365839	1,005 bp	37	38
	hRUP4	N.A.	AI307658	1,296 bp	39	40
25		N.A. = "not applicable".				

## 2. Full Length Cloning

### a. Human G2A

Mouse EST clone 1179426 was used to obtain a human genomic clone containing all

but three amino acid G2A coding sequences. The 5' of this coding sequence was obtained by using 5'RACE, and the template for PCR was Clontech's Human Spleen Marathon-Ready™ cDNA. The disclosed human G2A was amplified by PCR using the G2A cDNA specific primers for the first and second round PCR as shown in SEQ.ID.NO.: 41 and SEQ.ID.NO.:42

5 as follows:

5'-CTGTGTACAGCAGTTTCGAGAGTG-3' (SEQ.ID.NO.: 41; 1<sup>st</sup> round PCR)

5'-GAGTGCCAGGCAGAGCAGGTAGAC-3' (SEQ.ID.NO.: 42; second round PCR).

PCR was performed using Advantage GC Polymerase Kit (Clontech; manufacturing instructions will be followed), at 94°C for 30 sec followed by 5 cycles of 94°C for 5 sec and  
10 72°C for 4 min; and 30 cycles of 94° for 5 sec and 70° for 4 min. An approximate 1.3 Kb PCR fragment was purified from agarose gel, digested with Hind III and Xba I and cloned into the expression vector pRC/CMV2 (Invitrogen). The cloned-insert was sequenced using the T7 Sequenase™ kit (USB Amersham; manufacturer instructions followed) and the sequence was compared with the presented sequence. Expression of the human G2A was detected by  
15 probing an RNA dot blot (Clontech; manufacturer instructions followed) with the P<sup>32</sup>-labeled fragment.

#### b. CHN9

Sequencing of the EST clone 1541536 showed CHN9 to be a partial cDNA clone having only an initiation codon; *i.e.*, the termination codon was missing. When CHN9  
20 was used to blast against data base (nr), the 3' sequence of CHN9 was 100% homologous to the 5' untranslated region of the leukotriene B4 receptor cDNA, which contained a termination codon in the frame with CHN9 coding sequence. To determine whether the 5' untranslated region of LTB4R cDNA was the 3' sequence of CHN9, PCR was performed using primers based upon the 5' sequence flanking the initiation codon found in CHN9 and

the 3' sequence around the termination codon found in the LTB4R 5' untranslated region.

The 5' primer sequence utilized was as follows:

5'-CCCGAATTCCTGCTTGCTCCCAGCTTGGCCC-3' (SEQ.ID.NO.: 43; sense) and

5'-TGTGGATCCTGCTGTCAAAGGTCCCATTCGG-3' (SEQ.ID.NO.: 44; antisense).

- 5 PCR was performed using thymus cDNA as a template and rTth polymerase (Perkin Elmer) with the buffer system provided by the manufacturer, 0.25 uM of each primer, and 0.2 mM of each 4 nucleotides. The cycle condition was 30 cycles of 94°C for 1 min, 65°C for 1min and 72°C for 1 min and 10 sec. A 1.1kb fragment consistent with the predicted size was obtained from PCR. This PCR fragment was subcloned into pCMV (*see below*) and
- 10 sequenced (*see*, SEQ.ID.NO.: 35).

#### c. RUP 4

The full length RUP4 was cloned by RT-PCR with human brain cDNA (Clontech) as templates:

5'-TCACAATGCTAGGTGTGGTC-3' (SEQ.ID.NO.: 45; sense) and

- 15 5'-TGCATAGACAATGGGATTACAG-3' (SEQ.ID.NO.: 46; antisense).

PCR was performed using TaqPlus Precision™ polymerase (Stratagene; manufacturing instructions followed) by the following cycles: 94°C for 2 min; 94°C 30 sec; 55°C for 30 sec, 72°C for 45 sec, and 72°C for 10 min. Cycles 2 through 4 were repeated 30 times.

- The PCR products were separated on a 1% agarose gel and a 500 bp PCR fragment
- 20 was isolated and cloned into the pCRII-TOPO™ vector (Invitrogen) and sequenced using the T7 DNA Sequenase™ kit (Amsham) and the SP6/T7 primers (Stratagene). Sequence analysis revealed that the PCR fragment was indeed an alternatively spliced form of AI307658 having a continuous open reading frame with similarity to other GPCRs. The completed sequence of this PCR fragment was as follows:

5'-TCACAATGCTAGGTGTGGTCTGGCTGGTGGCAGTCATCGTAGGATCACCCATGTGGCAC  
GTGCAACAACCTTGAGATCAAATATGACTTCCTATATGAAAAGGAACACATCTGCTGCTTAAGA  
GTGGACCAGCCCTGTGCACCAGAAGATCTACACCACCTTCATCCTTGTCATCCTCTCCTCCTGC  
CTCTTATGGTGATGCTTATTCTGTACGTAAAATTGGTTATGAACCTTGGATAAAGAAAAGAGTT  
5 GGGGATGGTTCAGTGCTTCGAACTATTTCATGGAAAAGAAATGTCCAAAATAGCCAGGAAGAAG  
AAACGAGCTGTCATTATGATGGTGACAGTGGTGGCTCTCTTTGCTGTGTGCTGGGCACCATTC  
ATGTTGTCCATATGATGATTGAATACAGTAATTTGAAAAGGAATATGATGATGTCACAATCAA  
GATGATTTTGTCTATCGTGCAAATTATTGGATTTTCCAACCTCCATCTGTAATCCCATTGTCTATGCA-  
3' (SEQ.ID.NO.: 47)

- 10 Based on the above sequence, two sense oligonucleotide primer sets:

5'-CTGCTTAGAAGAGTGGACCAG-3' (SEQ.ID.NO.: 48; oligo 1),

5'-CTGTGCACCAGAAGATCTACAC-3' (SEQ.ID.NO.: 49; oligo 2) and

two antisense oligonucleotide primer sets:

5'-CAAGGATGAAGGTGGTGTAGA-3' (SEQ.ID.NO.: 50; oligo 3)

- 15 5'-GTGTAGATCTTCTGGTGCACAGG-3' (SEQ.ID.NO.: 51; oligo 4)

were used for 3'- and 5'-RACE PCR with a human brain Marathon-Ready™ cDNA (Clontech, Cat# 7400-1) as template, according to manufacture's instructions. DNA fragments generated by the RACE PCR were cloned into the pCRII-TOPO™ vector (Invitrogen) and sequenced using the SP6/T7 primers (Stratagene) and some internal primers.

- 20 The 3' RACE product contained a poly(A) tail and a completed open reading frame ending at a TAA stop codon. The 5' RACE product contained an incomplete 5' end; *i.e.*, the ATG initiation codon was not present.

Based on the new 5' sequence, oligo 3 and the following primer:

5'-GCAATGCAGGTCATAGTGAGC -3' (SEQ.ID.NO.: 52; oligo 5)

- 25 were used for the second round of 5' race PCR and the PCR products were analyzed as above.

A third round of 5' race PCR was carried out utilizing antisense primers:

5'-TGGAGCATGGTGACGGGAATGCAGAAG-3' (SEQ.ID.NO.: 53; oligo 6) and

5'-GTGATGAGCAGGTCAGTACGCGCCAAG-3' (SEQ.ID.NO.: 54; oligo 7).

The sequence of the 5' RACE PCR products revealed the presence of the initiation codon

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ATG, and further round of 5' race PCR did not generate any more 5' sequence. The completed 5' sequence was confirmed by RT-PCR using sense primer

5'-GCAATGCAGGCGCTTAACATTAC-3' (SEQ.ID.NO.: 55; oligo 8)

and oligo 4 as primers and sequence analysis of the 650 bp PCR product generated from

5 human brain and heart cDNA templates (Clontech, Cat# 7404-1). The completed 3' sequence was confirmed by RT-PCR using oligo 2 and the following antisense primer:

5'-TTGGGTTACAATCTGAAGGGCA-3' (SEQ.ID.NO.:56; oligo 9)

and sequence analysis of the 670 bp PCR product generated from human brain and heart cDNA templates. (Clontech, Cat# 7404-1).

10 **d. RUP5**

The full length RUP5 was cloned by RT-PCR using a sense primer upstream from ATG, the initiation codon (SEQ.ID.NO.:57), and an antisense primer containing TCA as the stop codon (SEQ.ID.NO.:58), which had the following sequences:

5'-ACTCCGTGTCCAGCAGGACTCTG-3' (SEQ.ID.NO.: 57)

15 5'-TGCGTGTTCTGGACCCTCACGTG-3' (SEQ.ID.NO.: 58)

and human peripheral leukocyte cDNA (Clontech) as a template. Advantage™ cDNA polymerase (Clontech) was used for the amplification in a 50ul reaction by the following cycle

with step 2 through step 4 repeated 30 times: 94°C for 30 sec; 94° for 15 sec; 69° for 40 sec;

72°C for 3 min; and 72°C fro 6 min. A 1.4kb PCR fragment was isolated and cloned with

20 the pCRII-TOPO™ vector (Invitrogen) and completely sequenced using the T7 DNA Sequenase™ kit (Amsham). See, SEQ.ID.NO.: 9.

**e. RUP6**

The full length RUP6 was cloned by RT-PCR using primers:

5'-CAGGCCTTGGATTTTAATGTCAGGGATGG-3' (SEQ.ID.NO.: 59) and

5'-GGAGAGTCAGCTCTGAAAGAATTCAGG-3' (SEQ.ID.NO.: 60);

and human thymus Marathon-Ready™ cDNA (Clontech) as a template. Advantage cDNA polymerase (Clontech, according to manufacturer's instructions) was used for the amplification in a 50ul reaction by the following cycle: 94°C for 30sec; 94°C for 5 sec; 66°C  
5 for 40sec; 72°C for 2.5 sec and 72°C for 7 min. Cycles 2 through 4 were repeated 30 times. A 1.3 Kb PCR fragment was isolated and cloned into the pCRII-TOPO™ vector (Invitrogen) and completely sequenced (*see*, SEQ.ID.NO.: 11) using the ABI Big Dye Terminator™ kit (P.E. Biosystem).

#### f. RUP7

10 The full length RUP7 was cloned by RT-PCR using primers:

5'-TGATGTGATGCCAGATACTAATAGCAC-3' (SEQ.ID.NO.: 61; sense) and

5'-CCTGATTCATTTAGGTGAGATTGAGAC-3' (SEQ.ID.NO.: 62; antisense)

and human peripheral leukocyte cDNA (Clontech) as a template. Advantage™ cDNA polymerase (Clontech) was used for the amplification in a 50 ul reaction by the following  
15 cycle with step 2 to step 4 repeated 30 times: 94°C for 2 minutes; 94°C for 15 seconds; 60°C for 20 seconds; 72°C for 2 minutes; 72°C for 10 minutes. A 1.25 Kb PCR fragment was isolated and cloned into the pCRII-TOPO™ vector (Invitrogen) and completely sequenced using the ABI Big Dye Terminator™ kit (P.E. Biosystem). *See*, SEQ.ID.NO.: 13.

#### 3. Angiotensin II Type 1 Receptor ("AT1")

20 The endogenous human angiotensin II type 1 receptor ("AT1") was obtained by PCR using genomic DNA as template and rTth polymerase (Perkin Elmer) with the buffer system provided by the manufacturer, 0.25 µM of each primer, and 0.2 mM of each 4 nucleotides. The cycle condition was 30 cycles of 94°C for 1 min, 55°C for 1min and 72°C for 1.5 min. The 5' PCR primer contains a HindIII site with the sequence:

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5'-CCCAAGCTTCCCCAGGTGTATTTGAT-3' (SEQ.ID.NO.: 63)

and the 3' primer contains a BamHI site with the following sequence:

5'-GTTGGATCCACATAATGCATTTTCTC-3' (SEQ.ID.NO.: 64).

The resulting 1.3 kb PCR fragment was digested with HindIII and BamHI and cloned into  
5 HindIII-BamHI site of pCMV expression vector. The cDNA clone was fully sequenced.  
Nucleic acid (SEQ.ID.NO.: 65) and amino acid (SEQ.ID.NO.: 66) sequences for human AT1  
were thereafter determined and verified.

#### 4. GPR38

To obtain GPR38, PCR was performed by combining two PCR fragments, using  
10 human genomic cDNA as template and rTth polymerase (Perkin Elmer) with the buffer system  
provided by the manufacturer, 0.25uM of each primer, and 0.2 mM of each 4 nucleotides.  
The cycle condition for each PCR reaction was 30 cycles of 94°C for 1 min, 62°C for 1min  
and 72°C for 2 min.

The first fragment was amplified with the 5' PCR primer that contained an end site  
15 with the following sequence:

5'-ACCATGGGCAGCCCCTGGAACGGCAGC-3' (SEQ.ID.NO.:67)

and a 3' primer having the following sequence:

5'-AGAACCACCACCAGCAGGACGCGGACGGTCTGCCGGTGG-3' (SEQ.ID.NO.:68).

The second PCR fragment was amplified with a 5' primer having the following sequence:

20 5'-GTCCGCGTCCTGCTGGTGGTGGTTCTGGCATTATAATT-3' (SEQ.ID.NO.: 69)

and a 3' primer that contained a BamHI site and having the following sequence:

5'-CCTGGATCCTTATCCCATCGTCTTCACGTTAGC-3' (SEQ.ID.NO.: 70).

The two fragments were used as templates to amplify GPR38, using SEQ.ID.NO.: 67 and  
SEQ.ID.NO.: 70 as primers (using the above-noted cycle conditions). The resulting 1.44kb



PCR fragment was digested with BamHI and cloned into Blunt-BamHI site of pCMV expression vector.

#### 5. MC4

To obtain MC4, PCR was performed using human genomic cDNA as template and  
5 rTth polymerase (Perkin Elmer) with the buffer system provided by the manufacturer, 0.25uM of each primer, and 0.2 mM of each 4 nucleotides. The cycle condition for each PCR reaction was 30 cycles of 94°C for 1 min, 54°C for 1min and 72°C for 1.5 min.

The 5' PCR contained an EcoRI site with the sequence:

5'-CTGGAATTCTCCTGCCAGCATGGTGA-3' (SEQ.ID.NO.: 71)

10 and the 3' primer contained a BamHI site with the sequence:

5'-GCAGGATCCTATATTGCGTGCTCTGTCCCC'-3 (SEQ.ID.NO.: 72).

The 1.0 kb PCR fragment was digest with EcoRI and BamHI and cloned into EcoRI-BamHI site of pCMV expression vector. Nucleic acid (SEQ.ID.NO.: 73) and amino acid (SEQ.ID.NO.: 74) sequences for human MC4 were thereafter determined.

#### 15 6. CCKB

To obtain CCKB, PCR was performed using human stomach cDNA as template and rTth polymerase (Perkin Elmer) with the buffer system provided by the manufacturer, 0.25uM of each primer, and 0.2 mM of each 4 nucleotides. The cycle condition for each PCR reaction was 30 cycles of 94°C for 1 min, 65°C for 1min and 72°C for 1 min and 30 sec.

20 The 5' PCR contained a HindIII site with the sequence:

5'-CCGAAGCTTCGAGCTGAGTAAGGCGGCGGGCT-3' (SEQ.ID.NO.: 75)

and the 3' primer contained an EcoRI site with the sequence:

5'-GTGGAATTCATTTGCCCTGCCTCAACCCCCA-3 (SEQ.ID.NO.: 76).

The resulting 1.44 kb PCR fragment was digest with HindIII and EcoRI and cloned into

HindIII-EcoRI site of pCMV expression vector. Nucleic acid (SEQ.ID.NO.: 77) and amino acid (SEQ.ID.NO.: 78) sequences for human CCKB were thereafter determined.

### 7. TDAG8

To obtain TDAG8, PCR was performed using genomic DNA as template and rTth polymerase (Perkin Elmer) with the buffer system provided by the manufacturer, 0.25  $\mu$ M of each primer, and 0.2 mM of each 4 nucleotides. The cycle condition was 30 cycles of 94°C for 1 min, 56°C for 1min and 72 °C for 1 min and 20 sec. The 5' PCR primer contained a HindIII site with the following sequence:

5'-TGCAAGCTTAAAAAGGAAAAAATGAACAGC-3' (SEQ.ID.NO.: 79)

and the 3' primer contained a BamHI site with the following sequence:

5'-TAAGGATCCCTTCCCTTCAAACATCCTTG -3' (SEQ.ID.NO.: 80).

The resulting 1.1 kb PCR fragment was digested with HindIII and BamHI and cloned into HindIII-BamHI site of pCMV expression vector. Three resulting clones sequenced contained three potential polymorphisms involving changes of amino acid 43 from Pro to Ala, amino acid 97 from Lys to Asn and amino acid 130 from Ile to Phe. Nucleic acid (SEQ.ID.NO.: 81) and amino acid (SEQ.ID.NO.: 82) sequences for human TDAG8 were thereafter determined.

### 8. H9

To obtain H9, PCR was performed using pituitary cDNA as template and rTth polymerase (Perkin Elmer) with the buffer system provided by the manufacturer, 0.25  $\mu$ M of each primer, and 0.2 mM of each 4 nucleotides. The cycle condition was 30 cycles of 94°C for 1 min, 62°C for 1 min and 72°C for 2 min. The 5' PCR primer contained a HindIII site with the following sequence:

5'-GGAAAGCTTAACGATCCCCAGGAGCAACAT-3' (SEQ.ID.NO.:15)

and the 3' primer contained a BamHI site with the following sequence:

5'-CTGGGATCCTACGAGAGCATTTTTCACACAG-3' (SEQ.ID.NO.:16).

The resulting 1.9 kb PCR fragment was digested with HindIII and BamHI and cloned into HindIII-BamHI site of pCMV expression vector. H9 contained three potential polymorphisms involving changes of amino acid P320S, S493N and amino acid G448A. Nucleic acid  
5 (SEQ.ID.NO.: 139) and amino acid (SEQ.ID.NO.: 140) sequences for human H9 were thereafter determined and verified.

### Example 2

#### PREPARATION OF NON-ENDOGENOUS, CONSTITUTIVELY ACTIVATED GPCRS

Those skilled in the art are credited with the ability to select techniques for  
10 mutation of a nucleic acid sequence. Presented below are approaches utilized to create non-endogenous versions of several of the human GPCRs disclosed above. The mutations disclosed below are based upon an algorithmic approach whereby the 16<sup>th</sup> amino acid (located in the IC3 region of the GPCR) from a conserved proline residue (located in the TM6 region of the GPCR, near the TM6/IC3 interface) is mutated, most preferably to a  
15 lysine amino acid residue.

##### 1. Transformer Site-Directed™ Mutagenesis

Preparation of non-endogenous human GPCRs may be accomplished on human GPCRs using Transformer Site-Directed™ Mutagenesis Kit (Clontech) according to the manufacturer instructions. Two mutagenesis primers are utilized, most preferably a lysine  
20 mutagenesis oligonucleotide that creates the lysine mutation, and a selection marker oligonucleotide. For convenience, the codon mutation to be incorporated into the human GPCR is also noted, in standard form (Table E):

TABLE E

	Receptor Identifier	Codon Mutation
	hARE-3	F313K
	hARE-4	V233K
5	hARE-5	A240K
	hGPCR14	L257K
	hGPCR27	C283K
	hARE-1	E232K
	hARE-2	G285K
10	hPPR1	L239K
	hG2A	K232A
	hRUP3	L224K
	hRUP5	A236K
	hRUP6	N267K
15	hRUP7	A302K
	hCHN4	V236K
	hMC4	A244K
	hCHN3	S284K
	hCHN6	L352K
20	hCHN8	N235K
	hCHN9	G223K
	hCHN10	L231K
	hH9	F236K

The following GPCRs were mutated according with the above method using the

25 designated sequence primers (Table F).

**TABLE F**

Receptor Identifier	Codon Mutation	Lysine Mutagenesis (SEQ.ID.NO.) 5'-3' orientation, mutation sequence underlined	Selection Marker (SEQ.ID.NO.) 5'-3' orientation
hRUP4	V272K	CAGGAAGAAG <u>AA</u> ACGAGC TGTCATTATGATGGTGACA GTG (83)	CACTGTCACCATCATAATG ACAGCTCGTTTCTTCTCC TG (84)
hAT1	<i>see below</i>	alternative approach; <i>see below</i>	alternative approach; <i>see below</i>
hGPR38	V297K	GGCCACCGGCAGACCA <u>AA</u> AC GCGTCCTGCTG (85)	CTCCTTCGGTCCTCCTATC GTTGTCAGAAGT (86)
hCCKB	V332K	alternative approach; <i>see below</i>	alternative approach; <i>see below</i>
hTDAG8	I225K	GGAAAAGAAGAGAATCAA <u>AAA</u> ACTACTTGTCAGCATC (87)	CTCCTTCGGTCCTCCTATC GTTGTCAGAAGT (88)
hH9	F236K	GCTGAGGTTTCGCAATA <u>AA</u> AC TAACCATGTTTGTG (143)	CTCCTTCGGTCCTCCTATC GTTGTCAGAAGT (144)
hMC4	A244K	GCCAATATGAAGGGAA <u>AA</u> A ATTACCTTGACCATC (137)	CTCCTTCGGTCCTCCTATC GTTGTCAGAAGT (138)

The non-endogenous human GPCRs were then sequenced and the derived and verified nucleic acid and amino acid sequences are listed in the accompanying "Sequence Listing" appendix to this patent document, as summarized in Table G below:

**TABLE G**

Non Endogenous Human GPCR	Nucleic Acid Sequence Listing	Amino Acid Sequence Listing
hRUP4 (V272K)	SEQ.ID.NO.: 127	SEQ.ID.NO.: 128
hAT1 ( <i>see alternative approaches below</i> )	( <i>see alternative approaches below</i> )	( <i>see alternative approaches below</i> )
hGPR38 (V297K)	SEQ.ID.NO.: 129	SEQ.ID.NO.: 130
hCCKB (V332K)	SEQ.ID.NO.: 131	SEQ.ID.NO.: 132
hTDAG8 (I225K)	SEQ.ID.NO.: 133	SEQ.ID.NO.: 134
hH9 (F236K)	SEQ.ID.NO.: 141	SEQ.ID.NO.: 142
hMC4 (A244K)	SEQ.ID.NO.: 135	SEQ.ID.NO.: 136

## 2. Alternative Approaches For Creation of Non-Endogenous Human GPCRs

### a. AT1

#### 1. F239K Mutation

Preparation of a non-endogenous, constitutively activated human AT1 receptor was accomplished by creating an F239K mutation (see, SEQ.ID.NO.: 89 for nucleic acid sequence, and SEQ.ID.NO.: 90 for amino acid sequence). Mutagenesis was performed using Transformer Site-Directed Mutagenesis™ Kit (Clontech) according to the to manufacturer's instructions. The two mutagenesis primers were used, a lysine mutagenesis oligonucleotide (SEQ.ID.NO.: 91) and a selection marker oligonucleotide (SEQ.ID.NO.: 92), which had the following sequences:

5'-CCAAGAAATGATGATATTA AAAAGATAATTATGGC-3' (SEQ.ID.NO.: 91)

5'-CTCCTTCGGTCCTCCTATCGTTGTCAGAAAGT-3' (SEQ.ID.NO.: 92),

respectively.

#### 2. N111A Mutation

Preparation of a non-endogenous human AT1 receptor was also accomplished by creating an N111A mutation (see, SEQ.ID.NO.:93 for nucleic acid sequence, and SEQ.ID.NO.: 94 for amino acid sequence). Two PCR reactions were performed using pfu polymerase (Stratagene) with the buffer system provided by the manufacturer, supplemented with 10% DMSO, 0.25 µM of each primer, and 0.5 mM of each 4 nucleotides. The 5' PCR sense primer used had the following sequence:

5'-CCCAAGCTTCCCCAGGTGTATTTGAT-3' (SEQ.ID.NO.: 95)

and the antisense primer had the following sequence:

5'-CCTGCAGGCGAAACTGACTCTGGCTGAAG-3' (SEQ.ID.NO.: 96).

The resulting 400 bp PCR fragment was digested with HindIII site and subcloned into HindIII-SmaI site of pCMV vector (5' construct). The 3' PCR sense primer used had the following sequence:

5 5'-CTGTACGCTAGTGTGTTTCTACTCACGTGTCTCAGCATTGAT-3' (SEQ.ID.NO.: 97)

and the antisense primer had the following sequence:.

5'-GTTGGATCCACATAATGCATTTTCTC-3' (SEQ.ID.NO.: 98)

The resulting 880 bp PCR fragment was digested with BamHI and inserted into Pst (blunted by T4 polymerase) and BamHI site of 5' construct to generated the full length

10 N111A construct. The cycle condition was 25 cycles of 94°C for 1 min, 60°C for 1min and 72°C for 1 min (5' PCR) or 1.5 min (3' PCR).

### 3. AT2K255IC3 Mutation

Preparation of a non-endogenous, constitutively activated human AT1 was accomplished by creating an AT2K255IC3 "domain swap" mutation (see, SEQ.ID.NO.:99 for nucleic acid sequence, and SEQ.ID.NO.: 100 for amino acid sequence). Restriction sites flanking IC3 of AT1 were generated to facilitate replacement of the IC3 with corresponding IC3 from angiotensin II type 2 receptor (AT2). This was accomplished by performing two PCR reactions. A 5' PCR fragment (Fragment A) encoded from the 5' untranslated region to the beginning of IC3 was generated by utilizing SEQ.ID.NO.: 63 as

20 sense primer and the following sequence:

5'-TCCGAATTCCAAAATAACTTGTAAGAATGATCAGAAA-3' (SEQ.ID.NO.: 101)

as antisense primer. A 3' PCR fragment (Fragment B) encoding from the end of IC3 to the 3' untranslated region was generated by using the following sequence:

5'-AGATCTTAAGAAGATAATTATGGCAATTGTGCT-3' (SEQ.ID.NO.: 102)

as sense primer and SEQ.ID.NO.: 64 as antisense primer. The PCR condition was 30 cycles of 94°C for 1 min, 55°C for 1min and 72°C for 1.5 min using endogenous AT1 cDNA clone as template and pfu polymerase (Stratagene), with the buffer systems provided by the manufacturer, supplemented with 10% DMSO, 0.25 µM of each primer, 5 and 0.5 mM of each 4 nucleotides. Fragment A (720 bp) was digested with HindIII and EcoRI and subcloned. Fragment B was digested with BamHI and subcloned into pCMV vector with an EcoRI site 5' to the cloned PCR fragment.

The DNA fragment (Fragment C) encoding IC3 of AT2 with a L255K mutation and containing an EcoRI cohesive end at 5' and a AflII cohesive end at 3', was generated by annealing 2 synthetic oligonucleotides having the following sequences:

5'AATTCGAAAACACTTACTGAAGACGAATAGCTATGGGAAGAACAGGATAACCCGTGACCAAG-3' (sense; SEQ.ID.NO.: 103)

5'TTAAGTTGGTCACGGGTTATCCTGTTCTCCCATAGCTATTCGTCTTCAGT  
15 AAGTGTTCG-3' (antisense; SEQ.ID.NO.: 104).

Fragment C was inserted in front of Fragment B through EcoRI and AflII site. The resulting clone was then ligated with the Fragment A through the EcoRI site to generate AT1 with AT2K255IC3.

#### 4. A243+ Mutation

20 Preparation of a non-endogenous human AT1 receptor was also accomplished by creating an A243+ mutation (see, SEQ.ID.NO.: 105 for nucleic acid sequence, and SEQ.ID.NO.: 106 for amino acid sequence). An A243+ mutation was constructed using the following PCR based strategy: Two PCR reactions was performed using pfu polymerase (Stratagene) with the buffer system provided by the manufacturer supplemented with 10%  
25 DMSO, 0.25 µM of each primer, and 0.5 mM of each 4 nucleotides. The 5' PCR sense primer



utilized had the following sequence:

5'-CCCAAGCTTCCCCAGGTGTATTTGAT-3' (SEQ.ID.NO.: 107)

and the antisense primer had the following sequence:

5'-AAGCACAATTGCTGCATAATTATCTTAAAAATATCATC-3' (SEQ.ID.NO.: 108).

- 5 The 3' PCR sense primer utilized had the following sequence:

5'-AAGATAATTATGGCAGCAATTGTGCTTTTCTTTTCTTT-3' (SEQ.ID.NO.: 109)

containing the Ala insertion and antisense primer:

5'-GTTGGATCCACATAATGCATTTTCTC-3' (SEQ.ID.NO.: 110).

The cycle condition was 25 cycles of 94°C for 1 min, 54°C for 1 min and 72°C for 1.5 min.

- 10 An aliquot of the 5' and 3' PCR were then used as co-template to perform secondary PCR using the 5' PCR sense primer and 3' PCR antisense primer. The PCR condition was the same as primary PCR except the extension time was 2.5 min. The resulting PCR fragment was digested with HindIII and BamHI and subcloned into pCMV vector. (See, SEQ.ID.NO.: 105)

15 **4. CCKB**

Preparation of the non-endogenous, constitutively activated human CCKB receptor was accomplished by creating a V322K mutation (see, SEQ.ID.NO.: 111 for nucleic acid sequence and SEQ.ID.NO.: 112 for amino acid sequence). Mutagenesis was performed by PCR via amplification using the wildtype CCKB from Example 1.

- 20 The first PCR fragment (1kb) was amplified by using SEQ.ID.NO.: 75 and an antisense primer comprising a V322K mutation:

5'-CAGCAGCATGCGCTTACGCGCTTCTTAGCCCAG-3' (SEQ.ID.NO.: 113).

The second PCR fragment (0.44kb) was amplified by using a sense primer comprising the V322K mutation:

5'-AGAAGCGCGTGAAGCGCATGCTGCTGGTGATCGTT-3' (SEQ.ID.NO.: 114) and SEQ.ID.NO.: 76.

The two resulting PCR fragments were then used as template for amplifying CCKB comprising V332K, using SEQ.ID.NO.: 75 and SEQ.ID.NO.: 76 and the above-noted system and conditions. The resulting 1.44kb PCR fragment containing the V332K mutation was digested with HindIII and EcoRI and cloned into HindIII-EcoRI site of pCMV expression vector. (See, SEQ.ID.NO.: 111).

### 3. QuikChange™ Site-Directed™ Mutagenesis

Preparation of non-endogenous human GPCRs can also be accomplished by using QuikChange™ Site-Directed™ Mutagenesis Kit (Stratagene, according to manufacturer's instructions). Endogenous GPCR is preferably used as a template and two mutagenesis primers utilized, as well as, most preferably, a lysine mutagenesis oligonucleotide and a selection marker oligonucleotide (included in kit). For convenience, the codon mutation incorporated into the human GPCR and the respective oligonucleotides are noted, in standard form (Table H):

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a first mutation of the human receptor if (a) the level of constitutive activation of the subsequent mutated form of a human receptor is substantially the same as that evidenced by the first mutation of the receptor; and (b) the percent sequence (amino acid and/or nucleic acid) homology between the subsequent mutated form of the receptor and the first mutation of the receptor is at least about 80%, more preferably at least about 90% and most preferably at least 95%. Ideally, and owing to the fact that the most preferred cassettes disclosed herein for achieving constitutive activation includes a single amino acid and/or codon change between the endogenous and the non-endogenous forms of the GPCR, the percent sequence homology should be at least 98%.

10       **NON-ORPHAN RECEPTOR** shall mean an endogenous naturally occurring molecule specific for an endogenous naturally occurring ligand wherein the binding of a ligand to a receptor activates an intracellular signaling pathway.

**ORPHAN RECEPTOR** shall mean an endogenous receptor for which the endogenous ligand specific for that receptor has not been identified or is not known.

15       **PHARMACEUTICAL COMPOSITION** shall mean a composition comprising at least one active ingredient, whereby the composition is amenable to investigation for a specified, efficacious outcome in a mammal (for example, and not limitation, a human). Those of ordinary skill in the art will understand and appreciate the techniques appropriate for determining whether an active ingredient has a desired efficacious outcome based upon the  
20   needs of the artisan.

**PLASMID** shall mean the combination of a Vector and cDNA. Generally, a Plasmid is introduced into a Host Cell for the purposes of replication and/or expression of the cDNA as a protein.

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**STIMULATE** or **STIMULATING**, in relationship to the term "response" shall mean that a response is increased in the presence of a compound as opposed to in the absence of the compound.

**VECTOR** in reference to cDNA shall mean a circular DNA capable of incorporating  
5 at least one cDNA and capable of incorporation into a Host Cell.

The order of the following sections is set forth for presentational efficiency and is not intended, nor should be construed, as a limitation on the disclosure or the claims to follow.

**A. Introduction**

The traditional study of receptors has always proceeded from the a priori assumption  
10 (historically based) that the endogenous ligand must first be identified before discovery could proceed to find antagonists and other molecules that could affect the receptor. Even in cases where an antagonist might have been known first, the search immediately extended to looking for the endogenous ligand. This mode of thinking has persisted in receptor research even after the discovery of constitutively activated receptors. What has not been heretofore recognized  
15 is that it is the active state of the receptor that is most useful for discovering agonists, partial agonists, and inverse agonists of the receptor. For those diseases which result from an overly active receptor or an under-active receptor, what is desired in a therapeutic drug is a compound which acts to diminish the active state of a receptor or enhance the activity of the receptor, respectively, not necessarily a drug which is an antagonist to the endogenous ligand.  
20 This is because a compound that reduces or enhances the activity of the active receptor state need not bind at the same site as the endogenous ligand. Thus, as taught by a method of this invention, any search for therapeutic compounds should start by screening compounds against the ligand-independent active state.

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**B. Identification of Human GPCRs**

The efforts of the Human Genome project has led to the identification of a plethora of information regarding nucleic acid sequences located within the human genome; it has been the case in this endeavor that genetic sequence information has been made available without an understanding or recognition as to whether or not any particular genomic sequence does or may contain open-reading frame information that translate human proteins. Several methods of identifying nucleic acid sequences within the human genome are within the purview of those having ordinary skill in the art. For example, and not limitation, a variety of human GPCRs, disclosed herein, were discovered by reviewing the GenBank™ database, while other GPCRs were discovered by utilizing a nucleic acid sequence of a GPCR, previously sequenced, to conduct a BLAST™ search of the EST database. Table B, below, lists several endogenous GPCRs that we have discovered, along with a GPCR's respective homologous receptor.

**TABLE B**

	Disclosed Human Orphan GPCRs	Accession Number Identified	Open Reading Frame (Base Pairs)	Per Cent Homology To Designated GPCR	Reference To Homologous GPCR (Accession No.)
15					
	hARE-3	AL033379	1,260 bp	52.3% LPA-R	U92642
20	hARE-4	AC006087	1,119 bp	36% P2Y5	AF000546
	hARE-5	AC006255	1,104 bp	32% <i>Oryzias latipes</i>	D43633
	hGPR27	AA775870	1,128 bp		
	hARE-1	AI090920	999 bp	43% KIAA0001	D13626
	hARE-2	AA359504	1,122 bp	53% GPR27	
25	hPPR1	H67224	1,053 bp	39% EBI1	L31581
	hG2A	AA754702	1,113 bp	31% GPR4	L36148

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	<b>hRUP3</b>	AL035423	1,005 bp	30% <i>Drosophila melanogaster</i>	2133653
	<b>hRUP4</b>	AI307658	1,296 bp	32% pNPGPR 28% and 29 % <i>Zebra fish</i> Ya and Yb, respectively	NP_004876 AAC41276 and AAB94616
	<b>hRUP5</b>	AC005849	1,413 bp	25% DEZ 23% FMLPR	Q99788 P21462
5	<b>hRUP6</b>	AC005871	1,245 bp	48% GPR66	NP_006047
	<b>hRUP7</b>	AC007922	1,173 bp	43% H3R	AF140538
	<b>hCHN3</b>	EST 36581	1,113 bp	53% GPR27	
	<b>hCHN4</b>	AA804531	1,077 bp	32% thrombin	4503637
	<b>hCHN6</b>	EST 2134670	1,503 bp	36% edg-1	NP_001391
	<b>hCHN8</b>	EST 764455	1,029 bp	47% KIAA0001	D13626
10	<b>hCHN9</b>	EST 1541536	1,077 bp	41% LTB4R	NM_000752
	<b>hCHN10</b>	EST 1365839	1,055 bp	35% P2Y	NM_002563

Receptor homology is useful in terms of gaining an appreciation of a role of the receptors within the human body. As the patent document progresses, we will disclose techniques for mutating these receptors to establish non-endogenous, constitutively activated versions of these receptors.

The techniques disclosed herein have also been applied to other human, orphan GPCRs known to the art, as will be apparent as the patent document progresses.

### C. Receptor Screening

Screening candidate compounds against a non-endogenous, constitutively activated version of the human GPCRs disclosed herein allows for the direct identification of candidate compounds which act at this cell surface receptor, without requiring use of the receptor's endogenous ligand. By determining areas within the body where the endogenous version of human GPCRs disclosed herein is expressed and/or over-expressed, it is possible to determine related disease/disorder states which are associated with the expression and/or over-expression

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of the receptor; such an approach is disclosed in this patent document.

With respect to creation of a mutation that may evidence constitutive activation of the human GPCR disclosed herein is based upon the distance from the proline residue at which is presumed to be located within TM6 of the GPCR; this algorithmic technique is disclosed  
5 in co-pending and commonly assigned patent document U.S. Serial Number 09/170,496, incorporated herein by reference. The algorithmic technique is not predicated upon traditional sequence "alignment" but rather a specified distance from the aforementioned TM6 proline residue. By mutating the amino acid residue located 16 amino acid residues from this residue (presumably located in the IC3 region of the receptor) to, most preferably, a lysine residue,  
10 such activation may be obtained. Other amino acid residues may be useful in the mutation at this position to achieve this objective.

#### **D. Disease/Disorder Identification and/or Selection**

As will be set forth in greater detail below, most preferably inverse agonists to the non-endogenous, constitutively activated GPCR can be identified by the methodologies of this  
15 invention. Such inverse agonists are ideal candidates as lead compounds in drug discovery programs for treating diseases related to this receptor. Because of the ability to directly identify inverse agonists to the GPCR, thereby allowing for the development of pharmaceutical compositions, a search for diseases and disorders associated with the GPCR is relevant. For example, scanning both diseased and normal tissue samples for the presence  
20 of the GPCR now becomes more than an academic exercise or one which might be pursued along the path of identifying an endogenous ligand to the specific GPCR. Tissue scans can be conducted across a broad range of healthy and diseased tissues. Such tissue scans provide a preferred first step in associating a specific receptor with a disease and/or disorder. *See, for*

*example*, co-pending application (docket number ARE-0050) for exemplary dot-blot and RT-PCR results of several of the GPCRs disclosed herein.

Preferably, the DNA sequence of the human GPCR is used to make a probe for (a) dot-blot analysis against tissue-mRNA, and/or (b) RT-PCR identification of the expression  
5 of the receptor in tissue samples. The presence of a receptor in a tissue source, or a diseased tissue, or the presence of the receptor at elevated concentrations in diseased tissue compared to a normal tissue, can be preferably utilized to identify a correlation with a treatment regimen, including but not limited to, a disease associated with that disease. Receptors can equally well be localized to regions of organs by this technique. Based on  
10 the known functions of the specific tissues to which the receptor is localized, the putative functional role of the receptor can be deduced.

#### **E. Screening of Candidate Compounds**

##### **1. Generic GPCR screening assay techniques**

When a G protein receptor becomes constitutively active, it binds to a G protein (*e.g.*,  
15 Gq, Gs, Gi, Gz, Go) and stimulates the binding of GTP to the G protein. The G protein then acts as a GTPase and slowly hydrolyzes the GTP to GDP, whereby the receptor, under normal conditions, becomes deactivated. However, constitutively activated receptors continue to exchange GDP to GTP. A non-hydrolyzable analog of GTP, [<sup>35</sup>S]GTPγS, can be used to monitor enhanced binding to membranes which express constitutively activated receptors.  
20 It is reported that [<sup>35</sup>S]GTPγS can be used to monitor G protein coupling to membranes in the absence and presence of ligand. An example of this monitoring, among other examples well-known and available to those in the art, was reported by Traynor and Nahorski in 1995. The preferred use of this assay system is for initial screening of candidate compounds because the



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system is generically applicable to all G protein-coupled receptors regardless of the particular G protein that interacts with the intracellular domain of the receptor.

## 2. Specific GPCR screening assay techniques

Once candidate compounds are identified using the "generic" G protein-coupled receptor assay (*i.e.*, an assay to select compounds that are agonists, partial agonists, or inverse agonists), further screening to confirm that the compounds have interacted at the receptor site is preferred. For example, a compound identified by the "generic" assay may not bind to the receptor, but may instead merely "uncouple" the G protein from the intracellular domain.

### a. *Gs, Gz and Gi.*

10       Gs stimulates the enzyme adenylyl cyclase. Gi (and Gz and Go), on the other hand, inhibit this enzyme. Adenylyl cyclase catalyzes the conversion of ATP to cAMP; thus, constitutively activated GPCRs that couple the Gs protein are associated with increased cellular levels of cAMP. On the other hand, constitutively activated GPCRs that couple Gi (or Gz, Go) protein are associated with decreased cellular levels of cAMP. *See, generally,*

15       "Indirect Mechanisms of Synaptic Transmission," Chpt. 8, From Neuron To Brain (3<sup>rd</sup> Ed.) Nichols, J.G. et al eds. Sinauer Associates, Inc. (1992). Thus, assays that detect cAMP can be utilized to determine if a candidate compound is, *e.g.*, an inverse agonist to the receptor (*i.e.*, such a compound would decrease the levels of cAMP). A variety of approaches known

20       in the art for measuring cAMP can be utilized; a most preferred approach relies upon the use of anti-cAMP antibodies in an ELISA-based format. Another type of assay that can be utilized is a whole cell second messenger reporter system assay. Promoters on genes drive the expression of the proteins that a particular gene encodes. Cyclic AMP drives gene expression by promoting the binding of a cAMP-responsive DNA binding protein or

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transcription factor (CREB) that then binds to the promoter at specific sites called cAMP response elements and drives the expression of the gene. Reporter systems can be constructed which have a promoter containing multiple cAMP response elements before the reporter gene, *e.g.*,  $\beta$ -galactosidase or luciferase. Thus, a constitutively activated Gs-linked receptor causes the accumulation of cAMP that then activates the gene and expression of the reporter protein. The reporter protein such as  $\beta$ -galactosidase or luciferase can then be detected using standard biochemical assays (Chen et al. 1995).

*b. Go and Gq.*

Gq and Go are associated with activation of the enzyme phospholipase C, which in turn hydrolyzes the phospholipid  $PIP_2$ , releasing two intracellular messengers: diacylglycerol (DAG) and inistol 1,4,5-triphoisphate ( $IP_3$ ). Increased accumulation of  $IP_3$  is associated with activation of Gq- and Go-associated receptors. *See, generally, "Indirect Mechanisms of Synaptic Transmission," Chpt. 8, From Neuron To Brain (3<sup>rd</sup> Ed.) Nichols, J.G. et al eds. Sinauer Associates, Inc. (1992).* Assays that detect  $IP_3$  accumulation can be utilized to determine if a candidate compound is, *e.g.*, an inverse agonist to a Gq- or Go-associated receptor (*i.e.*, such a compound would decrease the levels of  $IP_3$ ). Gq-associated receptors can also been examined using an AP1 reporter assay in that Gq-dependent phospholipase C causes activation of genes containing AP1 elements; thus, activated Gq-associated receptors will evidence an increase in the expression of such genes, whereby inverse agonists thereto will evidence a decrease in such expression, and agonists will evidence an increase in such expression. Commercially available assays for such detection are available.

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### 3. GPCR Fusion Protein

The use of an endogenous, constitutively activate orphan GPCR or a non-endogenous, constitutively activated orphan GPCR, for use in screening of candidate compounds for the direct identification of inverse agonists, agonists and partial agonists provide an interesting  
5 screening challenge in that, by definition, the receptor is active even in the absence of an endogenous ligand bound thereto. Thus, in order to differentiate between, *e.g.*, the non-endogenous receptor in the presence of a candidate compound and the non-endogenous receptor in the absence of that compound, with an aim of such a differentiation to allow for an understanding as to whether such compound may be an inverse agonist, agonist, partial  
10 agonist or have no affect on such a receptor, it is preferred that an approach be utilized that can enhance such differentiation. A preferred approach is the use of a GPCR Fusion Protein.

Generally, once it is determined that a non-endogenous orphan GPCR has been constitutively activated using the assay techniques set forth above (as well as others), it is possible to determine the predominant G protein that couples with the endogenous GPCR.  
15 Coupling of the G protein to the GPCR provides a signaling pathway that can be assessed. Because it is most preferred that screening take place by use of a mammalian expression system, such a system will be expected to have endogenous G protein therein. Thus, by definition, in such a system, the non-endogenous, constitutively activated orphan GPCR will continuously signal. In this regard, it is preferred that this signal be enhanced such that in the  
20 presence of, *e.g.*, an inverse agonist to the receptor, it is more likely that it will be able to more readily differentiate, particularly in the context of screening, between the receptor when it is contacted with the inverse agonist.

The GPCR Fusion Protein is intended to enhance the efficacy of G protein coupling

with the non-endogenous GPCR. The GPCR Fusion Protein is preferred for screening with a non-endogenous, constitutively activated GPCR because such an approach increases the signal that is most preferably utilized in such screening techniques. This is important in facilitating a significant "signal to noise" ratio; such a significant ratio is import preferred for  
5 the screening of candidate compounds as disclosed herein.

The construction of a construct useful for expression of a GPCR Fusion Protein is within the purview of those having ordinary skill in the art. Commercially available expression vectors and systems offer a variety of approaches that can fit the particular needs of an investigator. The criteria of importance for such a GPCR Fusion Protein construct is  
10 that the endogenous GPCR sequence and the G protein sequence both be in-frame (preferably, the sequence for the endogenous GPCR is upstream of the G protein sequence) and that the "stop" codon of the GPCR must be deleted or replaced such that upon expression of the GPCR, the G protein can also be expressed. The GPCR can be linked directly to the G protein, or there can be spacer residues between the two (preferably, no more than about 12,  
15 although this number can be readily ascertained by one of ordinary skill in the art). We have a preference (based upon convenience) of use of a spacer in that some restriction sites that are not used will, effectively, upon expression, become a spacer. Most preferably, the G protein that couples to the non-endogenous GPCR will have been identified prior to the creation of the GPCR Fusion Protein construct. Because there are only a few G proteins that have been  
20 identified, it is preferred that a construct comprising the sequence of the G protein (*i.e.*, a universal G protein construct) be available for insertion of an endogenous GPCR sequence therein; this provides for efficiency in the context of large-scale screening of a variety of different endogenous GPCRs having different sequences.

As noted above, constitutively activated GPCRs that couple to Gi, Gz and Go are expected to inhibit the formation of cAMP making assays based upon these types of GPCRs challenging (*i.e.*, the cAMP signal decreases upon activation thus making the direct identification of, *e.g.*, inverse agonists (which would further decrease this signal), interesting).

- 5 As will be disclosed herein, we have ascertained that for these types of receptors, it is possible to create a GPCR Fusion Protein that is not based upon the endogenous GPCR's endogenous G protein, in an effort to establish a viable cyclase-based assay. Thus, for example, a Gz coupled receptor such as H9, a GPCR Fusion Protein can be established that utilizes a Gs fusion protein – we believe that such a fusion construct, upon expression, "drives" or "forces"
- 10 the non-endogenous GPCR to couple with, *e.g.*, Gs rather than the "natural" Gz protein, such that a cyclase-based assay can be established. Thus, for Gi, Gz and Go coupled receptors, we prefer that that when a GPCR Fusion Protein is used and the assay is based upon detection of adenylyl cyclase activity, that the fusion construct be established with Gs (or an equivalent G protein that stimulates the formation of the enzyme adenylyl cyclase).

15 **F. Medicinal Chemistry**

- Generally, but not always, direct identification of candidate compounds is preferably conducted in conjunction with compounds generated via combinatorial chemistry techniques, whereby thousands of compounds are randomly prepared for such analysis. Generally, the results of such screening will be compounds having unique core structures; thereafter, these
- 20 compounds are preferably subjected to additional chemical modification around a preferred core structure(s) to further enhance the medicinal properties thereof. Such techniques are known to those in the art and will not be addressed in detail in this patent document.

### G. Pharmaceutical compositions

Candidate compounds selected for further development can be formulated into pharmaceutical compositions using techniques well known to those in the art. Suitable pharmaceutically-acceptable carriers are available to those in the art; for example, see  
5 Remington's Pharmaceutical Sciences, 16<sup>th</sup> Edition, 1980, Mack Publishing Co., (Oslo et al., eds.)

### H. Other Utility

Although a preferred use of the non-endogenous versions the human GPCRs disclosed herein may be for the direct identification of candidate compounds as inverse agonists,  
10 agonists or partial agonists (preferably for use as pharmaceutical agents), these versions of human GPCRs can also be utilized in research settings. For example, *in vitro* and *in vivo* systems incorporating GPCRs can be utilized to further elucidate and understand the roles these receptors play in the human condition, both normal and diseased, as well as understanding the role of constitutive activation as it applies to understanding the signaling  
15 cascade. The value in non-endogenous human GPCRs is that their utility as a research tool is enhanced in that, because of their unique features, non-endogenous human GPCRs can be used to understand the role of these receptors in the human body before the endogenous ligand therefor is identified. Other uses of the disclosed receptors will become apparent to those in the art based upon, *inter alia*, a review of this patent document.

20

### EXAMPLES

The following examples are presented for purposes of elucidation, and not limitation, of the present invention. While specific nucleic acid and amino acid sequences are disclosed herein, those of ordinary skill in the art are credited with the ability to make minor

modifications to these sequences while achieving the same or substantially similar results reported below. The traditional approach to application or understanding of sequence cassettes from one sequence to another (e.g. from rat receptor to human receptor or from human receptor A to human receptor B) is generally predicated upon sequence alignment techniques whereby the sequences are aligned in an effort to determine areas of commonality. The mutational approach disclosed herein does not rely upon this approach but is instead based upon an algorithmic approach and a positional distance from a conserved proline residue located within the TM6 region of human GPCRs. Once this approach is secured, those in the art are credited with the ability to make minor modifications thereto to achieve substantially the same results (i.e., constitutive activation) disclosed herein. Such modified approaches are considered within the purview of this disclosure

### Example 1

#### ENDOGENOUS HUMAN GPCRS

##### 1. Identification of Human GPCRs

Certain of the disclosed endogenous human GPCRs were identified based upon a review of the GenBank™ database information. While searching the database, the following cDNA clones were identified as evidenced below (Table C).

TABLE C

Disclosed Human Orphan GPCRs	Accession Number	Complete DNA Sequence (Base Pairs)	Open Reading Frame (Base Pairs)	Nucleic Acid SEQ.ID. NO.	Amino Acid SEQ.ID. NO.
hARE-3	AL033379	111,389 bp	1,260 bp	1	2
hARE-4	AC006087	226,925 bp	1,119 bp	3	4
hARE-5	AC006255	127,605 bp	1,104 bp	5	6
hRUP3	AL035423	140,094 bp	1,005 bp	7	8

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hRUP5	AC005849	169,144 bp	1,413 bp	9	10
hRUP6	AC005871	218,807 bp	1,245 bp	11	12
hRUP7	AC007922	158,858 bp	1,173 bp	13	14

Other disclosed endogenous human GPCRs were identified by conducting a BLAST™  
 5 search of EST database (dbest) using the following EST clones as query sequences. The  
 following EST clones identified were then used as a probe to screen a human genomic library  
 (Table D).

TABLE D

	Disclosed Human Orphan GPCRs	Query (Sequence)	EST Clone/ Accession No. Identified	Open Reading Frame (Base Pairs)	Nucleic Acid SEQ.ID.NO.	Amino Acid SEQ.ID.NO.
10	hGPCR27	Mouse GPCR27	AA775870	1,125 bp	17	18
	hARE-1	TDAG	1689643 A1090920	999 bp	19	20
15	hARE-2	GPCR27	68530 AA359504	1,122 bp	21	22
	hPPR1	Bovine PPR1	238667 H67224	1,053 bp	23	24
	hG2A	Mouse 1179426	<i>See Example 2(a), below</i>	1,113 bp	25	26
	hCHN3	N.A.	EST 36581 (full length)	1,113 bp	27	28
	hCHN4	TDAG	1184934 AA804531	1,077 bp	29	30
20	hCHN6	N.A.	EST 2134670 (full length)	1,503 bp	31	32
	hCHN8	K1AA0001	EST 764455	1,029 bp	33	34
	hCHN 9	1365839	EST 1541536	1,077 bp	35	36
	hCHN10	Mouse EST 1365839	Human 1365839	1,005 bp	37	38
	hRUP4	N.A.	AI307658	1,296 bp	39	40
25		N.A. = "not applicable".				

## 2. Full Length Cloning

### a. Human G2A

Mouse EST clone 1179426 was used to obtain a human genomic clone containing all



but three amino acid G2A coding sequences. The 5' of this coding sequence was obtained by using 5'RACE, and the template for PCR was Clontech's Human Spleen Marathon-Ready™ cDNA. The disclosed human G2A was amplified by PCR using the G2A cDNA specific primers for the first and second round PCR as shown in SEQ.ID.NO.: 41 and SEQ.ID.NO.:42

5 as follows:

5'-CTGTGTACAGCAGTTCGCAGAGTG-3' (SEQ.ID.NO.: 41; 1<sup>st</sup> round PCR)

5'-GAGTGCCAGGCAGAGCAGGTAGAC-3' (SEQ.ID.NO.: 42; second round PCR).

PCR was performed using Advantage GC Polymerase Kit (Clontech; manufacturing instructions will be followed), at 94°C for 30 sec followed by 5 cycles of 94°C for 5 sec and  
10 72°C for 4 min; and 30 cycles of 94° for 5 sec and 70° for 4 min. An approximate 1.3 Kb PCR fragment was purified from agarose gel, digested with Hind III and Xba I and cloned into the expression vector pRC/CMV2 (Invitrogen). The cloned-insert was sequenced using the T7 Sequenase™ kit (USB Amersham; manufacturer instructions followed) and the sequence was compared with the presented sequence. Expression of the human G2A was detected by  
15 probing an RNA dot blot (Clontech; manufacturer instructions followed) with the P<sup>32</sup>-labeled fragment.

#### b. CHN9

Sequencing of the EST clone 1541536 showed CHN9 to be a partial cDNA clone having only an initiation codon; *i.e.*, the termination codon was missing. When CHN9  
20 was used to blast against data base (nr), the 3' sequence of CHN9 was 100% homologous to the 5' untranslated region of the leukotriene B4 receptor cDNA, which contained a termination codon in the frame with CHN9 coding sequence. To determine whether the 5' untranslated region of LTB4R cDNA was the 3' sequence of CHN9, PCR was performed using primers based upon the 5' sequence flanking the initiation codon found in CHN9 and

the 3' sequence around the termination codon found in the LTB4R 5' untranslated region.

The 5' primer sequence utilized was as follows:

5'-CCCGAATTCCTGCTTGCTCCCAGCTTGGCCC-3' (SEQ.ID.NO.: 43; sense) and

5'-TGTGGATCCTGCTGTCAAAGGTCCCATTCCGG-3' (SEQ.ID.NO.: 44; antisense).

- 5 PCR was performed using thymus cDNA as a template and rTth polymerase (Perkin Elmer) with the buffer system provided by the manufacturer, 0.25  $\mu$ M of each primer, and 0.2 mM of each 4 nucleotides. The cycle condition was 30 cycles of 94°C for 1 min, 65°C for 1min and 72 °C for 1 min and 10 sec. A 1.1kb fragment consistent with the predicted size was obtained from PCR. This PCR fragment was subcloned into pCMV (*see below*) and
- 10 sequenced (*see*, SEQ.ID.NO.: 35).

#### c. RUP 4

The full length RUP4 was cloned by RT-PCR with human brain cDNA (Clontech) as templates:

5'-TCACAATGCTAGGTGTGGTC-3' (SEQ.ID.NO.: 45; sense) and

- 15 5'-TGCATAGACAATGGGATTACAG-3' (SEQ.ID.NO.: 46; antisense).

PCR was performed using TaqPlus Precision™ polymerase (Stratagene; manufacturing instructions followed) by the following cycles: 94°C for 2 min; 94°C 30 sec; 55°C for 30 sec, 72°C for 45 sec, and 72°C for 10 min. Cycles 2 through 4 were repeated 30 times.

- The PCR products were separated on a 1% agarose gel and a 500 bp PCR fragment
- 20 was isolated and cloned into the pCRII-TOPO™ vector (Invitrogen) and sequenced using the T7 DNA Sequenase™ kit (Amsham) and the SP6/T7 primers (Stratagene). Sequence analysis revealed that the PCR fragment was indeed an alternatively spliced form of AI307658 having a continuous open reading frame with similarity to other GPCRs. The completed sequence of this PCR fragment was as follows:

5'-TCACAATGCTAGGTGTGGTCTGGCTGGTGGCAGTCATCGTAGGATCACCCATGTGGCAC  
GTGCAACAACCTTGAGATCAAATATGACTTCCTATATGAAAAGGAACACATCTGCTGCTTAAGA  
GTGGACCAGCCCTGTGCACCAGAAGATCTACACCACCTTCATCCTTGTCATCCTCTTCCTCCTGC  
CTCTTATGGTGATGCTTATTCTGTACGTAAAAATTGGTTATGAACTTTGGATAAAGAAAAGAGTT  
5 GGGGATGGTTTCAGTGCTTCGAACTATTCATGGAAAAGAAATGTCCAAAATAGCCAGGAAGAAG  
AAACGAGCTGTCATTATGATGGTGACAGTGGTGGCTCTCTTTGCTGTGTGCTGGGCACCATTC  
ATGTTGTCCATATGATGATTGAATACAGTAATTTTGGAAAAGGAATATGATGATGTCACAATCAA  
GATGATTTTGTCTATCGTGCAAATTATTGGATTTTCCAACCTCCATCTGTAATCCCATTGTCTATGCA-  
3' (SEQ.ID.NO.: 47)

10 Based on the above sequence, two sense oligonucleotide primer sets:

5'-CTGCTTAGAAGAGTGGACCAG-3' (SEQ.ID.NO.: 48; oligo 1),

5'-CTGTGCACCAGAAGATCTACAC-3' (SEQ.ID.NO.: 49; oligo 2) and

two antisense oligonucleotide primer sets:

5'-CAAGGATGAAGGTGGTGTAGA-3' (SEQ.ID.NO.: 50; oligo 3)

15 5'-GTGTAGATCTTCTGGTGCACAGG-3' (SEQ.ID.NO.: 51; oligo 4)

were used for 3'- and 5'-RACE PCR with a human brain Marathon-Ready™ cDNA (Clontech, Cat# 7400-1) as template, according to manufacture's instructions. DNA fragments generated by the RACE PCR were cloned into the pCRII-TOPO™ vector (Invitrogen) and sequenced using the SP6/T7 primers (Stratagene) and some internal primers.

20 The 3' RACE product contained a poly(A) tail and a completed open reading frame ending at a TAA stop codon. The 5' RACE product contained an incomplete 5' end; *i.e.*, the ATG initiation codon was not present.

Based on the new 5' sequence, oligo 3 and the following primer:

5'-GCAATGCAGGTCATAGTGAGC -3' (SEQ.ID.NO.: 52; oligo 5)

25 were used for the second round of 5' race PCR and the PCR products were analyzed as above.

A third round of 5' race PCR was carried out utilizing antisense primers:

5'-TGGAGCATGGTGACGGGAATGCAGAAG-3' (SEQ.ID.NO.: 53; oligo 6) and

5'-GTGATGAGCAGGTCACTGAGCGCCAAG-3' (SEQ.ID.NO.: 54; oligo 7).

The sequence of the 5' RACE PCR products revealed the presence of the initiation codon

ATG, and further round of 5' race PCR did not generate any more 5' sequence. The completed 5' sequence was confirmed by RT-PCR using sense primer

5'-GCAATGCAGGCGCTTAACATTAC-3' (SEQ.ID.NO.: 55; oligo 8)

and oligo 4 as primers and sequence analysis of the 650 bp PCR product generated from

5 human brain and heart cDNA templates (Clontech, Cat# 7404-1). The completed 3' sequence was confirmed by RT-PCR using oligo 2 and the following antisense primer:

5'-TTGGGTTACAATCTGAAGGGCA-3' (SEQ.ID.NO.:56; oligo 9)

and sequence analysis of the 670 bp PCR product generated from human brain and heart cDNA templates. (Clontech, Cat# 7404-1).

#### 10 d. RUP5

The full length RUP5 was cloned by RT-PCR using a sense primer upstream from ATG, the initiation codon (SEQ.ID.NO.:57), and an antisense primer containing TCA as the stop codon (SEQ.ID.NO.:58), which had the following sequences:

5'-ACTCCGTGTCCAGCAGGACTCTG-3' (SEQ.ID.NO.: 57)

15 5'-TGCGTGTTCTGGACCCTCACGTG-3' (SEQ.ID.NO.: 58)

and human peripheral leukocyte cDNA (Clontech) as a template. Advantage™ cDNA polymerase (Clontech) was used for the amplification in a 50ul reaction by the following cycle with step 2 through step 4 repeated 30 times: 94°C for 30 sec; 94° for 15 sec; 69° for 40 sec; 72°C for 3 min; and 72°C fro 6 min. A 1.4kb PCR fragment was isolated and cloned with  
20 the pCRII-TOPO™ vector (Invitrogen) and completely sequenced using the T7 DNA Sequenase™ kit (Amsham). See, SEQ.ID.NO.: 9.

#### e. RUP6

The full length RUP6 was cloned by RT-PCR using primers:

5'-CAGGCCTTGGATTTTAATGTCAGGGATGG-3' (SEQ.ID.NO.: 59) and

5'-GGAGAGTCAGCTCTGAAAGAATTCAGG-3' (SEQ.ID.NO.: 60);  
and human thymus Marathon-Ready™ cDNA (Clontech) as a template. Advantage cDNA polymerase (Clontech, according to manufacturer's instructions) was used for the amplification in a 50ul reaction by the following cycle: 94°C for 30sec; 94°C for 5 sec; 66°C  
5 for 40sec; 72°C for 2.5 sec and 72°C for 7 min. Cycles 2 through 4 were repeated 30 times. A 1.3 Kb PCR fragment was isolated and cloned into the pCRII-TOPO™ vector (Invitrogen) and completely sequenced (*see*, SEQ.ID.NO.: 11) using the ABI Big Dye Terminator™ kit (P.E. Biosystem).

#### f. RUP7

10 The full length RUP7 was cloned by RT-PCR using primers:  
5'-TGATGTGATGCCAGATACTAATAGCAC-3' (SEQ.ID.NO.: 61; sense) and  
5'-CCTGATTCATTTAGGTGAGATTGAGAC-3' (SEQ.ID.NO.: 62; antisense)  
and human peripheral leukocyte cDNA (Clontech) as a template. Advantage™ cDNA polymerase (Clontech) was used for the amplification in a 50 ul reaction by the following  
15 cycle with step 2 to step 4 repeated 30 times: 94°C for 2 minutes; 94°C for 15 seconds; 60°C for 20 seconds; 72°C for 2 minutes; 72°C for 10 minutes. A 1.25 Kb PCR fragment was isolated and cloned into the pCRII-TOPO™ vector (Invitrogen) and completely sequenced using the ABI Big Dye Terminator™ kit (P.E. Biosystem). *See*, SEQ.ID.NO.: 13.

### 3. Angiotensin II Type 1 Receptor ("AT1")

20 The endogenous human angiotensin II type 1 receptor ("AT1") was obtained by PCR using genomic DNA as template and rTth polymerase (Perkin Elmer) with the buffer system provided by the manufacturer, 0.25 µM of each primer, and 0.2 mM of each 4 nucleotides. The cycle condition was 30 cycles of 94°C for 1 min, 55°C for 1min and 72°C for 1.5 min. The 5' PCR primer contains a HindIII site with the sequence:

- 30 -

5'-CCCAAGCTTCCCCAGGTGTATTTGAT-3' (SEQ.ID.NO.: 63)

and the 3' primer contains a BamHI site with the following sequence:

5'-GTTGGATCCACATAATGCATTTTCTC-3' (SEQ.ID.NO.: 64).

The resulting 1.3 kb PCR fragment was digested with HindIII and BamHI and cloned into  
5 HindIII-BamHI site of pCMV expression vector. The cDNA clone was fully sequenced.  
Nucleic acid (SEQ.ID.NO.: 65) and amino acid (SEQ.ID.NO.: 66) sequences for human AT1  
were thereafter determined and verified.

#### 4. GPR38

To obtain GPR38, PCR was performed by combining two PCR fragments, using  
10 human genomic cDNA as template and rTth polymerase (Perkin Elmer) with the buffer system  
provided by the manufacturer, 0.25uM of each primer, and 0.2 mM of each 4 nucleotides.  
The cycle condition for each PCR reaction was 30 cycles of 94°C for 1 min, 62°C for 1min  
and 72°C for 2 min.

The first fragment was amplified with the 5' PCR primer that contained an end site  
15 with the following sequence:

5'-ACCATGGGCAGCCCCCTGGAACGGCAGC-3' (SEQ.ID.NO.:67)

and a 3' primer having the following sequence:

5'-AGAACCACCACCAGCAGGACGCGGACGGTCTGCCGGTGG-3' (SEQ.ID.NO.:68).

The second PCR fragment was amplified with a 5' primer having the following sequence:

20 5'-GTCCGCGTCCTGCTGGTGGTGGTTCTGGCATTATAATT-3' (SEQ.ID.NO.: 69)

and a 3' primer that contained a BamHI site and having the following sequence:

5'-CCTGGATCCTTATCCCATCGTCTTCACGTTAGC-3' (SEQ.ID.NO.: 70).

The two fragments were used as templates to amplify GPR38, using SEQ.ID.NO.: 67 and  
SEQ.ID.NO.: 70 as primers (using the above-noted cycle conditions). The resulting 1.44kb

PCR fragment was digested with BamHI and cloned into Blunt-BamHI site of pCMV expression vector.

#### 5. MC4

To obtain MC4, PCR was performed using human genomic cDNA as template and  
5 rTth polymerase (Perkin Elmer) with the buffer system provided by the manufacturer, 0.25uM of each primer, and 0.2 mM of each 4 nucleotides. The cycle condition for each PCR reaction was 30 cycles of 94°C for 1 min, 54°C for 1min and 72°C for 1.5 min.

The 5' PCR contained an EcoRI site with the sequence:

5'-CTGGAATTCTCCTGCCAGCATGGTGA-3' (SEQ.ID.NO.: 71)

10 and the 3' primer contained a BamHI site with the sequence:

5'-GCAGGATCCTATATTGCGTGCTCTGTCCC'-3 (SEQ.ID.NO.: 72).

The 1.0 kb PCR fragment was digest with EcoRI and BamHI and cloned into EcoRI-BamHI site of pCMV expression vector. Nucleic acid (SEQ.ID.NO.: 73) and amino acid (SEQ.ID.NO.: 74) sequences for human MC4 were thereafter determined.

#### 15 6. CCKB

To obtain CCKB, PCR was performed using human stomach cDNA as template and  
rTth polymerase (Perkin Elmer) with the buffer system provided by the manufacturer, 0.25uM of each primer, and 0.2 mM of each 4 nucleotides. The cycle condition for each PCR reaction was 30 cycles of 94°C for 1 min, 65°C for 1min and 72°C for 1 min and 30 sec.

20 The 5' PCR contained a HindIII site with the sequence:

5'-CCGAAGCTTCGAGCTGAGTAAGGCGGCGGGCT-3' (SEQ.ID.NO.: 75)

and the 3' primer contained an EcoRI site with the sequence:

5'-GTGGAATTCATTTGCCCTGCCTCAACCCCCA-3 (SEQ.ID.NO.: 76).

The resulting 1.44 kb PCR fragment was digest with HindIII and EcoRI and cloned into

HindIII-EcoRI site of pCMV expression vector. Nucleic acid (SEQ.ID.NO.: 77) and amino acid (SEQ.ID.NO.: 78) sequences for human CCKB were thereafter determined.

### 7. TDAG8

To obtain TDAG8, PCR was performed using genomic DNA as template and rTth polymerase (Perkin Elmer) with the buffer system provided by the manufacturer, 0.25  $\mu$ M of each primer, and 0.2 mM of each 4 nucleotides. The cycle condition was 30 cycles of 94°C for 1 min, 56°C for 1min and 72 °C for 1 min and 20 sec. The 5' PCR primer contained a HindIII site with the following sequence:

5'-TGCAAGCTTAAAAAGGAAAAATGAACAGC-3' (SEQ.ID.NO.: 79)

10 and the 3' primer contained a BamHI site with the following sequence:

5'-TAAGGATCCCTTCCCTTCAAAACATCCTTG -3' (SEQ.ID.NO.: 80).

The resulting 1.1 kb PCR fragment was digested with HindIII and BamHI and cloned into HindIII-BamHI site of pCMV expression vector. Three resulting clones sequenced contained three potential polymorphisms involving changes of amino acid 43 from Pro to Ala, amino acid 97 from Lys to Asn and amino acid 130 from Ile to Phe. Nucleic acid (SEQ.ID.NO.: 81) and amino acid (SEQ.ID.NO.: 82) sequences for human TDAG8 were thereafter determined.

### 8. H9

To obtain H9, PCR was performed using pituitary cDNA as template and rTth polymerase (Perkin Elmer) with the buffer system provided by the manufacturer, 0.25  $\mu$ M of each primer, and 0.2 mM of each 4 nucleotides. The cycle condition was 30 cycles of 94°C for 1 min, 62°C for 1 min and 72°C for 2 min. The 5' PCR primer contained a HindIII site with the following sequence:

5'-GGAAAGCTTAACGATCCCCAGGAGCAACAT-3' (SEQ.ID.NO.:15)

and the 3' primer contained a BamHI site with the following sequence:



5'-CTGGGATCCTACGAGAGCATTTTTCACACAG-3' (SEQ.ID.NO.:16).

The resulting 1.9 kb PCR fragment was digested with HindIII and BamHI and cloned into HindIII-BamHI site of pCMV expression vector. H9 contained three potential polymorphisms involving changes of amino acid P320S, S493N and amino acid G448A. Nucleic acid  
5 (SEQ.ID.NO.: 139) and amino acid (SEQ.ID.NO.: 140) sequences for human H9 were thereafter determined and verified.

## **Example 2**

### **PREPARATION OF NON-ENDOGENOUS, CONSTITUTIVELY ACTIVATED GPCRS**

Those skilled in the art are credited with the ability to select techniques for  
10 mutation of a nucleic acid sequence. Presented below are approaches utilized to create non-endogenous versions of several of the human GPCRs disclosed above. The mutations disclosed below are based upon an algorithmic approach whereby the 16<sup>th</sup> amino acid (located in the IC3 region of the GPCR) from a conserved proline residue (located in the TM6 region of the GPCR, near the TM6/IC3 interface) is mutated, most preferably to a  
15 lysine amino acid residue.

#### **1. Transformer Site-Directed <sup>TM</sup> Mutagenesis**

Preparation of non-endogenous human GPCRs may be accomplished on human GPCRs using Transformer Site-Directed<sup>TM</sup> Mutagenesis Kit (Clontech) according to the manufacturer instructions. Two mutagenesis primers are utilized, most preferably a lysine  
20 mutagenesis oligonucleotide that creates the lysine mutation, and a selection marker oligonucleotide. For convenience, the codon mutation to be incorporated into the human GPCR is also noted, in standard form (Table E):

TABLE E

	Receptor Identifier	Codon Mutation
	hARE-3	F313K
	hARE-4	V233K
5	hARE-5	A240K
	hGPCR14	L257K
	hGPCR27	C283K
	hARE-1	E232K
	hARE-2	G285K
10	hPPR1	L239K
	hG2A	K232A
	hRUP3	L224K
	hRUP5	A236K
	hRUP6	N267K
15	hRUP7	A302K
	hCHN4	V236K
	hMC4	A244K
	hCHN3	S284K
	hCHN6	L352K
20	hCHN8	N235K
	hCHN9	G223K
	hCHN10	L231K
	hH9	F236K

The following GPCRs were mutated according with the above method using the

25

designated sequence primers (Table F).

- 35 -

**TABLE F**

Receptor Identifier	Codon Mutation	Lysine Mutagenesis (SEQ.ID.NO.) 5'-3' orientation, mutation sequence underlined	Selection Marker (SEQ.ID.NO.) 5'-3' orientation
hRUP4	V272K	CAGGAAGAAGAAACGAGC TGTCATTATGATGGTGACA GTG (83)	CACTGTCACCATCATAATG ACAGCTCGTTTCTTCTTCC TG (84)
hAT1	see below	alternative approach; see below	alternative approach; see below
hGPR38	V297K	GGCCACCGGCAGACCAAAC GCGTCCTGCTG (85)	CTCCTTCGGTCCTCCTATC GTTGTCAGAAGT (86)
hCCKB	V332K	alternative approach; see below	alternative approach; see below
hTDAG8	I225K	GGAAAAGAAGAGAATCAA AAACTACTTGTGAGCATC (87)	CTCCTTCGGTCCTCCTATC GTTGTCAGAAGT (88)
hH9	F236K	GCTGAGGTTTCGCAATAAAC TAACCATGTTTGTG (143)	CTCCTTCGGTCCTCCTATC GTTGTCAGAAGT (144)
hMC4	A244K	GCCAAATGAAGGGAAA ATTACCTTGACCATC (137)	CTCCTTCGGTCCTCCTATC GTTGTCAGAAGT (138)

The non-endogenous human GPCRs were then sequenced and the derived and verified nucleic acid and amino acid sequences are listed in the accompanying "Sequence Listing" appendix to this patent document, as summarized in Table G below:

**TABLE G**

	Non Endogenous Human GPCR	Nucleic Acid Sequence Listing	Amino Acid Sequence Listing
15	hRUP4 (V272K)	SEQ.ID.NO.: 127	SEQ.ID.NO.: 128
20	hAT1 (see alternative approaches below)	(see alternative approaches below)	(see alternative approaches, below)
	hGPR38 (V297K)	SEQ.ID.NO.: 129	SEQ.ID.NO.: 130
25	hCCKB (V332K)	SEQ.ID.NO.: 131	SEQ.ID.NO.: 132
	hTDAG8 (I225K)	SEQ.ID.NO.: 133	SEQ.ID.NO.: 134
	hH9 (F236K)	SEQ.ID.NO.: 141	SEQ.ID.NO.: 142
30	hMC4 (A244K)	SEQ.ID.NO.: 135	SEQ.ID.NO.: 136

## 2. Alternative Approaches For Creation of Non-Endogenous Human GPCRs

### a. AT1

#### 1. F239K Mutation

Preparation of a non-endogenous, constitutively activated human AT1 receptor was accomplished by creating an F239K mutation (see, SEQ.ID.NO.: 89 for nucleic acid sequence, and SEQ.ID.NO.: 90 for amino acid sequence). Mutagenesis was performed using Transformer Site-Directed Mutagenesis™ Kit (Clontech) according to the to manufacturer's instructions. The two mutagenesis primers were used, a lysine mutagenesis oligonucleotide (SEQ.ID.NO.: 91) and a selection marker oligonucleotide (SEQ.ID.NO.: 92), which had the following sequences:

5'-CCAAGAAATGATGATATTAAGATAATTATGGC-3' (SEQ.ID.NO.: 91)

5'-CTCCTTCGGTCCTCCTATCGTTGTCAGAAGT-3' (SEQ.ID.NO.: 92),

respectively.

#### 2. N111A Mutation

Preparation of a non-endogenous human AT1 receptor was also accomplished by creating an N111A mutation (see, SEQ.ID.NO.:93 for nucleic acid sequence, and SEQ.ID.NO.: 94 for amino acid sequence). Two PCR reactions were performed using pfu polymerase (Stratagene) with the buffer system provided by the manufacturer, supplemented with 10% DMSO, 0.25  $\mu$ M of each primer, and 0.5 mM of each 4 nucleotides. The 5' PCR sense primer used had the following sequence:

5'-CCCAAGCTTCCCCAGGTGTATTTGAT-3' (SEQ.ID.NO.: 95)

and the antisense primer had the following sequence:

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5'-CCTGCAGGCGAAACTGACTCTGGCTGAAG-3' (SEQ.ID.NO.: 96).

The resulting 400 bp PCR fragment was digested with HindIII site and subcloned into HindIII-SmaI site of pCMV vector (5' construct). The 3' PCR sense primer used had the following sequence:

5 5'-CTGTACGCTAGTGTGTTTCTACTCACGTGTCTCAGCATTGAT-3' (SEQ.ID.NO.: 97)

and the antisense primer had the following sequence:

5'-GTTGGATCCACATAATGCATTTTCTC-3' (SEQ.ID.NO.: 98)

The resulting 880 bp PCR fragment was digested with BamHI and inserted into Pst (blunted by T4 polymerase) and BamHI site of 5' construct to generated the full length

10 N111A construct. The cycle condition was 25 cycles of 94°C for 1 min, 60°C for 1min and 72°C for 1 min (5' PCR) or 1.5 min (3' PCR).

### 3. AT2K255IC3 Mutation

Preparation of a non-endogenous, constitutively activated human AT1 was accomplished by creating an AT2K255IC3 "domain swap" mutation (see, SEQ.ID.NO.:99

15 for nucleic acid sequence, and SEQ.ID.NO.: 100 for amino acid sequence). Restriction sites flanking IC3 of AT1 were generated to facilitate replacement of the IC3 with corresponding IC3 from angiotensin II type 2 receptor (AT2). This was accomplished by performing two PCR reactions. A 5' PCR fragment (Fragment A) encoded from the 5' untranslated region to the beginning of IC3 was generated by utilizing SEQ.ID.NO.: 63 as  
20 sense primer and the following sequence:

5'-TCCGAATTCCAAAATAACTTGTAAGAATGATCAGAAA-3' (SEQ.ID.NO.: 101)

as antisense primer. A 3' PCR fragment (Fragment B) encoding from the end of IC3 to the 3' untranslated region was generated by using the following sequence:

5'-AGATCTTAAGAAGATAATTATGGCAATTGTGCT-3' (SEQ.ID.NO.: 102)

as sense primer and SEQ.ID.NO.: 64 as antisense primer. The PCR condition was 30 cycles of 94°C for 1 min, 55°C for 1min and 72°C for 1.5 min using endogenous AT1 cDNA clone as template and pfu polymerase (Stratagene), with the buffer systems provided by the manufacturer, supplemented with 10% DMSO, 0.25 µM of each primer, and 0.5 mM of each 4 nucleotides. Fragment A (720 bp) was digested with HindIII and EcoRI and subcloned. Fragment B was digested with BamHI and subcloned into pCMV vector with an EcoRI site 5' to the cloned PCR fragment.

The DNA fragment (Fragment C) encoding IC3 of AT2 with a L255K mutation and containing an EcoRI cohesive end at 5' and a AflII cohesive end at 3', was generated by annealing 2 synthetic oligonucleotides having the following sequences:

5'AATTCGAAAACACTTACTGAAGACGAATAGCTATGGGAAGAACAGGATAACCCGTGACCAA  
G-3' (sense; SEQ.ID.NO.: 103)

5'TTAACTTGGTCACGGGTTATCCTGTTCTCCCATAGCTATTCGTCTTCAGT  
AAGTGTTTTTCG-3' (antisense; SEQ.ID.NO.: 104).

Fragment C was inserted in front of Fragment B through EcoRI and AflII site. The resulting clone was then ligated with the Fragment A through the EcoRI site to generate AT1 with AT2K255IC3.

#### 4. A243+ Mutation

Preparation of a non-endogenous human AT1 receptor was also accomplished by creating an A243+ mutation (see, SEQ.ID.NO.: 105 for nucleic acid sequence, and SEQ.ID.NO.: 106 for amino acid sequence). An A243+ mutation was constructed using the following PCR based strategy: Two PCR reactions was performed using pfu polymerase (Stratagene) with the buffer system provided by the manufacturer supplemented with 10% DMSO, 0.25 µM of each primer, and 0.5 mM of each 4 nucleotides. The 5' PCR sense primer

utilized had the following sequence:

5'-CCCAAGCTTCCCCAGGTGTATTTGAT-3' (SEQ.ID.NO.: 107)

and the antisense primer had the following sequence:

5'-AAGCACAATTGCTGCATAATTATCTTAAAAATATCATC-3' (SEQ.ID.NO.: 108).

- 5 The 3' PCR sense primer utilized had the following sequence:

5'-AAGATAATTATGGCAGCAATTGTGCTTTTCTTTTCTTT-3' (SEQ.ID.NO.: 109)

containing the Ala insertion and antisense primer:

5'-GTTGGATCCACATAATGCATTTTCTC-3' (SEQ.ID.NO.: 110).

The cycle condition was 25 cycles of 94°C for 1 min, 54°C for 1min and 72°C for 1.5 min.

- 10 An aliquot of the 5' and 3' PCR were then used as co-template to perform secondary PCR using the 5' PCR sense primer and 3' PCR antisense primer. The PCR condition was the same as primary PCR except the extension time was 2.5 min. The resulting PCR fragment was digested with HindIII and BamHI and subcloned into pCMV vector. (See, SEQ.ID.NO.: 105)

15 **4. CCKB**

Preparation of the non-endogenous, constitutively activated human CCKB receptor was accomplished by creating a V322K mutation (see, SEQ.ID.NO.: 111 for nucleic acid sequence and SEQ.ID.NO.: 112 for amino acid sequence). Mutagenesis was performed by PCR via amplification using the wildtype CCKB from Example 1.

- 20 The first PCR fragment (1kb) was amplified by using SEQ.ID.NO.: 75 and an antisense primer comprising a V322K mutation:

5'-CAGCAGCATGCGCTTCACGCGCTTCTTAGCCCAG-3' (SEQ.ID.NO.: 113).

The second PCR fragment (0.44kb) was amplified by using a sense primer comprising the V322K mutation:

5'-AGAAGCGCGTGAAGCGCATGCTGCTGGTGATCGTT-3' (SEQ.ID.NO.: 114) and SEQ.ID.NO.:

76.

The two resulting PCR fragments were then used as template for amplifying CCKB comprising V332K, using SEQ.ID.NO.: 75 and SEQ.ID.NO.: 76 and the above-noted  
5 system and conditions. The resulting 1.44kb PCR fragment containing the V332K mutation was digested with HindIII and EcoRI and cloned into HindIII-EcoRI site of pCMV expression vector. (See, SEQ.ID.NO.: 111).

### 3. QuikChange™ Site-Directed™ Mutagenesis

Preparation of non-endogenous human GPCRs can also be accomplished by using  
10 QuikChange™ Site-Directed™ Mutagenesis Kit (Stratagene, according to manufacturer's instructions). Endogenous GPCR is preferably used as a template and two mutagenesis primers utilized, as well as, most preferably, a lysine mutagenesis oligonucleotide and a selection marker oligonucleotide (included in kit). For convenience, the codon mutation incorporated into the human GPCR and the respective oligonucleotides are noted, in standard  
15 form (Table H):



**TABLE H**

Receptor Identifier	Codon Mutation	Lysine Mutagenesis (SEQ.ID.NO.) 5'-3' orientation, mutation underlined	Selection Marker (SEQ.ID.NO.) 5'-3' orientation
hCHN3	S284K	ATGGAGAAAAGAATCAAAAGAA TGTCTATATA (115)	TATATAGAACATTCTTTT GATTCTTTCTCCAT (116)
hCHN6	L352K	CGCTCTCTGGCCTTGAAGCGCAC GCTCAGC (117)	GCTGAGCGTGCGCTTCA AGGCCAGAGAGCG (118)
5 hCHN8	N235K	CCCAGGAAAAAGGTGAAAGTCA AAGTTTTC (119)	GAAAACCTTTGACTTTCAC CTTTTTCCTGGG (120)
hCHN9	G223K	GGGGCGCGGGTGAAACGGCTGG TGAGC (121)	GCTCACCAGCCGTTTCA CCCGCGCCCC (122)
hCHN10	L231K	CCCCTTGAAAGCCTAAGAAGT GGTCATC (123)	GATGACCAAGTTCTTAG GCTTTTCAAGGGG (124)

### Example 3

#### RECEPTOR EXPRESSION

10           Although a variety of cells are available to the art for the expression of proteins, it is most preferred that mammalian cells be utilized. The primary reason for this is predicated upon practicalities, *i.e.*, utilization of, *e.g.*, yeast cells for the expression of a GPCR, while possible, introduces into the protocol a non-mammalian cell which may not (indeed, in the case of yeast, does not) include the receptor-coupling, genetic-mechanism and secretary

15 pathways that have evolved for mammalian systems - thus, results obtained in non-mammalian cells, while of potential use, are not as preferred as that obtained from mammalian cells. Of the mammalian cells, COS-7, 293 and 293T cells are particularly preferred, although the specific mammalian cell utilized can be predicated upon the particular needs of the artisan.

On day one,  $1 \times 10^7$  293T cells per 150mm plate were plated out. On day two, two

20 reaction tubes were prepared (the proportions to follow for each tube are per plate): tube A was prepared by mixing 20 $\mu$ g DNA (*e.g.*, pCMV vector; pCMV vector with receptor cDNA, etc.) in 1.2ml serum free DMEM (Irvine Scientific, Irvine, CA); tube B was

prepared by mixing 120 $\mu$ l lipofectamine (Gibco BRL) in 1.2ml serum free DMEM. Tubes A and B were admixed by inversions (several times), followed by incubation at room temperature for 30-45min. The admixture is referred to as the "transfection mixture".

Plated 293T cells were washed with 1XPBS, followed by addition of 10ml serum free  
5 DMEM. 2.4ml of the transfection mixture were added to the cells, followed by incubation for 4hrs at 37°C/5% CO<sub>2</sub>. The transfection mixture was removed by aspiration, followed by the addition of 25ml of DMEM/10% Fetal Bovine Serum. Cells were incubated at 37°C/5% CO<sub>2</sub>. After 72hr incubation, cells were harvested and utilized for analysis.

#### **Example 4**

#### **10 ASSAYS FOR DETERMINATION OF CONSTITUTIVE ACTIVITY OF NON-ENDOGENOUS GPCRS**

A variety of approaches are available for assessment of constitutive activity of the non-endogenous human GPCRs. The following are illustrative; those of ordinary skill in the art are credited with the ability to determine those techniques that are preferentially

15 beneficial for the needs of the artisan.

##### **1. Membrane Binding Assays: [<sup>35</sup>S]GTP $\gamma$ S Assay**

When a G protein-coupled receptor is in its active state, either as a result of ligand binding or constitutive activation, the receptor couples to a G protein and stimulates the release of GDP and subsequent binding of GTP to the G protein. The alpha subunit of the G  
20 protein-receptor complex acts as a GTPase and slowly hydrolyzes the GTP to GDP, at which point the receptor normally is deactivated. Constitutively activated receptors continue to exchange GDP for GTP. The non-hydrolyzable GTP analog, [<sup>35</sup>S]GTP $\gamma$ S, can be utilized to demonstrate enhanced binding of [<sup>35</sup>S]GTP $\gamma$ S to membranes expressing constitutively activated receptors. The advantage of using [<sup>35</sup>S]GTP $\gamma$ S binding to measure constitutive

activation is that: (a) it is generically applicable to all G protein-coupled receptors; (b) it is proximal at the membrane surface making it less likely to pick-up molecules which affect the intracellular cascade.

The assay utilizes the ability of G protein coupled receptors to stimulate [<sup>35</sup>S]GTPγS  
5 binding to membranes expressing the relevant receptors. The assay can, therefore, be used in the direct identification method to screen candidate compounds to known, orphan and constitutively activated G protein-coupled receptors. The assay is generic and has application to drug discovery at all G protein-coupled receptors.

The [<sup>35</sup>S]GTPγS assay can be incubated in 20 mM HEPES and between 1 and about  
10 20mM MgCl<sub>2</sub> (this amount can be adjusted for optimization of results, although 20mM is preferred) pH 7.4, binding buffer with between about 0.3 and about 1.2 nM [<sup>35</sup>S]GTPγS (this amount can be adjusted for optimization of results, although 1.2 is preferred ) and 12.5 to 75 μg membrane protein (*e.g.* COS-7 cells expressing the receptor; this amount can be adjusted for optimization, although 75μg is preferred) and 1 μM GDP (this amount can be changed for  
15 optimization) for 1 hour. Wheatgerm agglutinin beads (25 μl; Amersham) should then be added and the mixture incubated for another 30 minutes at room temperature. The tubes are then centrifuged at 1500 x g for 5 minutes at room temperature and then counted in a scintillation counter.

A less costly but equally applicable alternative has been identified which also meets  
20 the needs of large scale screening. Flash plates™ and Wallac™ scintistrips may be utilized to format a high throughput [<sup>35</sup>S]GTPγS binding assay. Furthermore, using this technique, the assay can be utilized for known GPCRs to simultaneously monitor tritiated ligand binding to the receptor at the same time as monitoring the efficacy via [<sup>35</sup>S]GTPγS binding. This is

possible because the Wallac beta counter can switch energy windows to look at both tritium and  $^{35}\text{S}$ -labeled probes. This assay may also be used to detect other types of membrane activation events resulting in receptor activation. For example, the assay may be used to monitor  $^{32}\text{P}$  phosphorylation of a variety of receptors (both G protein coupled and tyrosine kinase receptors). When the membranes are centrifuged to the bottom of the well, the bound  $^{35}\text{S}$ GTP $\gamma$ S or the  $^{32}\text{P}$ -phosphorylated receptor will activate the scintillant which is coated of the wells. Scinti<sup>®</sup> strips (Wallac) have been used to demonstrate this principle. In addition, the assay also has utility for measuring ligand binding to receptors using radioactively labeled ligands. In a similar manner, when the radiolabeled bound ligand is centrifuged to the bottom of the well, the scintistrip label comes into proximity with the radiolabeled ligand resulting in activation and detection.

## 2. Adenylyl Cyclase

A Flash Plate<sup>™</sup> Adenylyl Cyclase kit (New England Nuclear; Cat. No. SMP004A) designed for cell-based assays can be modified for use with crude plasma membranes. The Flash Plate wells contain a scintillant coating which also contains a specific antibody recognizing cAMP. The cAMP generated in the wells was quantitated by a direct competition for binding of radioactive cAMP tracer to the cAMP antibody. The following serves as a brief protocol for the measurement of changes in cAMP levels in membranes that express the receptors.

Transfected cells are harvested approximately three days after transfection. Membranes were prepared by homogenization of suspended cells in buffer containing 20mM HEPES, pH 7.4 and 10mM  $\text{MgCl}_2$ . Homogenization is performed on ice using a Brinkman Polytron<sup>™</sup> for approximately 10 seconds. The resulting homogenate is centrifuged at 49,000

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X g for 15 minutes at 4°C. The resulting pellet is then resuspended in buffer containing 20mM HEPES, pH 7.4 and 0.1 mM EDTA, homogenized for 10 seconds, followed by centrifugation at 49,000 X g for 15 minutes at 4°C. The resulting pellet can be stored at -80°C until utilized. On the day of measurement, the membrane pellet is slowly thawed at room temperature, resuspended in buffer containing 20mM HEPES, pH 7.4 and 10mM MgCL<sub>2</sub> (these amounts can be optimized, although the values listed herein are preferred), to yield a final protein concentration of 0.60mg/ml (the resuspended membranes were placed on ice until use).

cAMP standards and Detection Buffer (comprising 2 µCi of tracer [<sup>125</sup>I cAMP (100 µl] to 11 ml Detection Buffer) are prepared and maintained in accordance with the manufacturer's instructions. Assay Buffer is prepared fresh for screening and contained 20mM HEPES, pH 7.4, 10mM MgCL<sub>2</sub>, 20mM (Sigma), 0.1 units/ml creatine phosphokinase (Sigma), 50 µM GTP (Sigma), and 0.2 mM ATP (Sigma); Assay Buffer can be stored on ice until utilized. The assay is initiated by addition of 50ul of assay buffer followed by addition of 50ul of membrane suspension to the NEN Flash Plate. The resultant assay mixture is incubated for 60 minutes at room temperature followed by addition of 100ul of detection buffer. Plates are then incubated an additional 2-4 hours followed by counting in a Wallac MicroBeta™ scintillation counter. Values of cAMP/well are extrapolated from a standard cAMP curve that is contained within each assay plate.

## 20 C. Reporter-Based Assays

### 1. CREB Reporter Assay (Gs-associated receptors)

A method to detect Gs stimulation depends on the known property of the transcription factor CREB, which is activated in a cAMP-dependent manner. A PathDetect™ CREB trans-

Reporting System (Stratagene, Catalogue # 219010) can utilized to assay for Gs coupled activity in 293 or 293T cells. Cells are transfected with the plasmids components of this above system and the indicated expression plasmid encoding endogenous or mutant receptor using a Mammalian Transfection Kit (Stratagene, Catalogue #200285) according to the  
5 manufacturer's instructions. Briefly, 400 ng pFR-Luc (luciferase reporter plasmid containing Gal4 recognition sequences), 40 ng pFA2-CREB (Gal4-CREB fusion protein containing the Gal4 DNA-binding domain), 80 ng pCMV-receptor expression plasmid (comprising the receptor) and 20 ng CMV-SEAP (secreted alkaline phosphatase expression plasmid; alkaline phosphatase activity is measured in the media of transfected cells to control for variations in  
10 transfection efficiency between samples) are combined in a calcium phosphate precipitate as per the Kit's instructions. Half of the precipitate is equally distributed over 3 wells in a 96-well plate, kept on the cells overnight, and replaced with fresh medium the following morning. Forty-eight (48) hr after the start of the transfection, cells are treated and assayed for, *e.g.*, luciferase activity

15                   2.     **AP1 reporter assay (Gq-associated receptors)**

A method to detect Gq stimulation depends on the known property of Gq-dependent phospholipase C to cause the activation of genes containing AP1 elements in their promoter. A Pathdetect™ AP-1 cis-Reporting System (Stratagene, Catalogue # 219073) can be utilized following the protocol set forth above with respect to the CREB reporter assay. except that  
20 the components of the calcium phosphate precipitate were 410 ng pAP1-Luc. 80 ng pCMV-receptor expression plasmid, and 20 ng CMV-SEAP.

                  3.     **CRE-LUC Reporter Assay**

293 and 293T cells are plated-out on 96 well plates at a density of  $2 \times 10^4$  cells per

well and were transfected using Lipofectamine Reagent (BRL) the following day according to manufacturer instructions. A DNA/lipid mixture is prepared for each 6-well transfection as follows: 260ng of plasmid DNA in 100 $\mu$ l of DMEM were gently mixed with 2 $\mu$ l of lipid in 100 $\mu$ l of DMEM (the 260ng of plasmid DNA consisted of 200ng of a 8xCRE-Luc reporter plasmid (*see* below and Figure 1 for a representation of a portion of the plasmid), 50ng of pCMV comprising endogenous receptor or non-endogenous receptor or pCMV alone, and 10ng of a GPRS expression plasmid (GPRS in pcDNA3 (Invitrogen)). The 8xCRE-Luc reporter plasmid was prepared as follows: vector SRIF- $\beta$ -gal was obtained by cloning the rat somatostatin promoter (-71/+51) at BglV-HindIII site in the p $\beta$ gal-Basic Vector (Clontech).

10 Eight (8) copies of cAMP response element were obtained by PCR from an adenovirus template AdpCF126CCRE8 (*see, 7 Human Gene Therapy* 1883 (1996)) and cloned into the SRIF- $\beta$ -gal vector at the Kpn-BglV site, resulting in the 8xCRE- $\beta$ -gal reporter vector. The 8xCRE-Luc reporter plasmid was generated by replacing the beta-galactosidase gene in the 8xCRE- $\beta$ -gal reporter vector with the luciferase gene obtained from the pGL3-basic vector

15 (Promega) at the HindIII-BamHI site. Following 30 min. incubation at room temperature, the DNA/lipid mixture was diluted with 400  $\mu$ l of DMEM and 100 $\mu$ l of the diluted mixture was added to each well. 100  $\mu$ l of DMEM with 10% FCS were added to each well after a 4hr incubation in a cell culture incubator. The following day the transfected cells were changed with 200  $\mu$ l/well of DMEM with 10% FCS. Eight (8) hours later, the wells were changed to

20 100  $\mu$ l /well of DMEM without phenol red, after one wash with PBS. Luciferase activity were measured the next day using the LucLite™ reporter gene assay kit (Packard) following manufacturer instructions and read on a 1450 MicroBeta™ scintillation and luminescence counter (Wallac).

#### 4. SRF-LUC Reporter Assay

One method to detect Gq stimulation depends on the known property of Gq-dependent phospholipase C to cause the activation of genes containing serum response factors in their promoter. A Pathdetect™ SRF-Luc-Reporting System (Stratagene) can be utilized to assay  
5 for Gq coupled activity in, *e.g.*, COS7 cells. Cells are transfected with the plasmid components of the system and the indicated expression plasmid encoding endogenous or non-endogenous GPCR using a Mammalian Transfection™ Kit (Stratagene, Catalogue #200285) according to the manufacturer's instructions. Briefly, 410 ng SRF-Luc, 80 ng pCMV-receptor expression plasmid and 20 ng CMV-SEAP (secreted alkaline phosphatase expression plasmid;  
10 alkaline phosphatase activity is measured in the media of transfected cells to control for variations in transfection efficiency between samples) are combined in a calcium phosphate precipitate as per the manufacturer's instructions. Half of the precipitate is equally distributed over 3 wells in a 96-well plate, kept on the cells in a serum free media for 24 hours. The last 5 hours the cells are incubated with 1  $\mu$ M Angiotensin, where indicated. Cells are then lysed  
15 and assayed for luciferase activity using a Lucite™ Kit (Packard, Cat. # 6016911) and "Trilux 1450 Microbeta" liquid scintillation and luminescence counter (Wallac) as per the manufacturer's instructions. The data can be analyzed using GraphPad Prism™ 2.0a (GraphPad Software Inc.).

#### 5. Intracellular IP<sub>3</sub> Accumulation Assay

20 On day 1, cells comprising the receptors (endogenous and/or non-endogenous) can be plated onto 24 well plates, usually  $1 \times 10^5$  cells/well (although this number can be optimized. On day 2 cells can be transfected by firstly mixing 0.25  $\mu$ g DNA in 50  $\mu$ l serum free DMEM/well and 2  $\mu$ l lipofectamine in 50  $\mu$ l serumfree DMEM/well. The solutions



are gently mixed and incubated for 15-30 min at room temperature. Cells are washed with 0.5 ml PBS and 400  $\mu$ l of serum free media is mixed with the transfection media and added to the cells. The cells are then incubated for 3-4 hrs at 37°C/5%CO<sub>2</sub>, and then the transfection media is removed and replaced with 1ml/well of regular growth media. On

5 day 3 the cells are labeled with <sup>3</sup>H-myo-inositol. Briefly, the media is removed and the cells are washed with 0.5 ml PBS. Then 0.5 ml inositol-free/serum free media (GIBCO BRL) is added/well with 0.25  $\mu$ Ci of <sup>3</sup>H-myo-inositol / well and the cells are incubated for 16-18 hrs o/n at 37°C/5%CO<sub>2</sub>. On Day 4 the cells are washed with 0.5 ml PBS and 0.45 ml of assay medium is added containing inositol-free/serum free media 10  $\mu$ M pargyline

10 10 mM lithium chloride or 0.4 ml of assay medium and 50  $\mu$ l of 10x ketanserin (ket) to final concentration of 10 $\mu$ M. The cells are then incubated for 30 min at 37°C. The cells are then washed with 0.5 ml PBS and 200  $\mu$ l of fresh/icecold stop solution (1M KOH; 18 mM Na-borate; 3.8 mM EDTA) is added/well. The solution is kept on ice for 5-10 min or until cells were lysed and then neutralized by 200  $\mu$ l of fresh/ice cold neutralization sol.

15 (7.5 % HCL). The lysate is then transferred into 1.5 ml eppendorf tubes and 1 ml of chloroform/methanol (1:2) is added/tube. The solution is vortexed for 15 sec and the upper phase is applied to a Biorad AG1-X8™ anion exchange resin (100-200 mesh). Firstly, the resin is washed with water at 1:1.25 W/V and 0.9 ml of upper phase is loaded onto the column. The column is washed with 10 mls of 5 mM myo-inositol and 10 ml of 5

20 mM Na-borate/60mM Na-formate. The inositol tris phosphates are eluted into scintillation vials containing 10 ml of scintillation cocktail with 2 ml of 0.1 M formic acid/ 1 M ammonium formate. The columns are regenerated by washing with 10 ml of 0.1 M formic acid/3M ammonium formate and rinsed twice with dd H<sub>2</sub>O and stored at 4°C in water.

Exemplary results are presented below in Table I:

TABLE I

Receptor	Mutation	Assay Utilized	Signal Generated: Endogenous Version (Relative Light Units)	Signal Generated: Non-Endogenous Version (Relative Light Units)	Percent Difference
hAT1	F239K	SRF-LUC	34	137	75%†
	AT2K255IC3	SRF-LUC	34	127	73%†
5 hTDAG8	I225K	CRE-LUC (293 cells)	2,715	14,440	81%†
	I225K	CRE-LUC (293T cells)	65,681	185,636	65%†
hH9 hCCKB	F236K	CRE-LUC	1,887	6,096	69%†
	V332K	CRE-LUC	785	3,223	76%†

### C. CELL-BASED DETECTION ASSAY (EXAMPLE -TDAG8)

10        293 cells were plated-out on 150mm plates at a density of  $1.3 \times 10^7$  cells per plate, and were transfected using 12ug of the respective DNA and 60ul of Lipofectamine Reagent (BRL) per plate. The transfected cells were grown in media containing serum for an assay performed 24 hours post-transfection. For detection assay performed 48 hours post-transfection (assay comparing serum and serum-free media; see Figure 3), the initial media  
15        was changed to either serum or serum-free media. The serum-free media was comprised solely of Dulbecco's Modified Eagle's (DME) High Glucose Medium (Irvine Scientific #9024). In addition to the above DME Medium, the media with serum contained the following: 10% Fetal Bovine Serum (Hyclone #SH30071.03), 1% of 100mM Sodium Pyruvate (Irvine Scientific #9334), 1% of 20mM L-Glutamine (Irvine Scientific #9317), and 1% of Penicillin-

Streptomycin solution (Irvine Scientific #9366).

A 96-well Adenylyl Cyclase Activation Flashplate™ was used (NEN: #SMP004A). First, 50ul of the standards for the assay were added to the plate, in duplicate, ranging from concentrations of 50pmol to zero pmol cAMP per well. The standard cAMP (NEN: #SMP004A) was reconstituted in water, and serial dilutions were made using 1xPBS (Irvine Scientific: #9240). Next, 50ul of the stimulation buffer (NEN: #SMP004A) was added to all wells. In the case of using compounds to measure activation or inactivation of cAMP, 10ul of each compound, diluted in water, was added to its respective well, in triplicate. Various final concentrations used range from 1uM up to 1mM. Adenosine 5'-triphosphate, ATP, (Research Biochemicals International: #A-141) and Adenosine 5'-diphosphate, ADP, (Sigma: #A2754) were used in the assay. Next, the 293 cells transfected with the respective cDNA (CMV or TDAG8) were harvested 24 (assay detection in serum media) or 48 hours post-transfection (assay detection comparing serum and serum-free media). The media was aspirated and the cells washed once with 1xPBS. Then 5ml of 1xPBS was added to the cells along with 3ml of cell dissociation buffer (Sigma: #C-1544). The detached cells were transferred to a centrifuge tube and centrifuged at room temperature for five minutes. The supernatant was removed and the cell pellet was resuspended in an appropriate amount of 1xPBS to obtain a final concentration of  $2 \times 10^6$  cells per milliliter. To the wells containing the compound, 50ul of the cells in 1xPBS ( $1 \times 10^5$  cells/well) were added. The plate was incubated on a shaker for 15 minutes at room temperature. The detection buffer containing the tracer cAMP was prepared. In 11ml of detection buffer (NEN: #SMP004A), 50ul (equal to 1uCi) of [<sup>125</sup>I]cAMP (NEN: #SMP004A) was added. Following incubation, 50ul of this detection buffer containing tracer cAMP was added to each well. The plate was placed on a shaker and

incubated at room temperature for two hours. Finally, the solution from the wells of the plate were aspirated and the flashplate was counted using the Wallac MicroBeta™ scintillation counter.

In Figure 2A, ATP and ADP bind to endogenous TDAG8 resulting in an increase  
5 of cAMP of about 59% and about 55% respectively. Figure 2B evidences ATP and ADP binding to endogenous TDAG8 where endogenous TDAG8 was transfected and grown in serum and serum-free medium. ATP binding to endogenous TDAG8 grown in serum media evidences an increase in cAMP of about 65%, compared to the endogenous TDAG8 with no compounds; in serum-free media there was an increase of about 68%. ADP  
10 binding to endogenous TDAG8 in serum evidences about a 61% increase, while in serum-free ADP binding evidences an increase of about 62% increase. ATP and ADP bind to endogenous TDAG8 with an EC50 value of 139.8uM and 120.5uM, respectively (data not shown).

Although the results presented in Figure 2B indicate substantially the same results  
15 when serum and serum-free media were compared, our choice is to use a serum based media, although a serum-free media can also be utilized.

#### **Example 6** **GPCR FUSION PROTEIN PREPARATION**

The design of the constitutively activated GPCR-G protein fusion construct was  
20 accomplished as follows: both the 5' and 3' ends of the rat G protein Gsα (long form; Itoh. H. et al., 83 *PNAS* 3776 (1986)) were engineered to include a HindIII (5'-AAGCTT-3') sequence thereon. Following confirmation of the correct sequence (including the flanking HindIII sequences), the entire sequence was shuttled into pcDNA3.1(-) (Invitrogen, cat. no. V795-20) by subcloning using the HindIII restriction site of that vector. The correct

orientation for the Gs $\alpha$  sequence was determined after subcloning into pcDNA3.1(-). The modified pcDNA3.1(-) containing the rat Gs $\alpha$  gene at HindIII sequence was then verified; this vector was now available as a "universal" Gs $\alpha$  protein vector. The pcDNA3.1(-) vector contains a variety of well-known restriction sites upstream of the HindIII site, thus  
5 beneficially providing the ability to insert, upstream of the Gs protein, the coding sequence of an endogenous, constitutively active GPCR. This same approach can be utilized to create other "universal" G protein vectors, and, of course, other commercially available or proprietary vectors known to the artisan can be utilized -- the important criteria is that the sequence for the GPCR be upstream and in-frame with that of the G protein.

10 TDAG8 couples via Gs, while H9 couples via Gz. For the following exemplary GPCR Fusion Proteins, fusion to Gs $\alpha$  was accomplished.

A TDAG8(I225K)-Gs $\alpha$  Fusion Protein construct was made as follows: primers were designed as follows:

5'-gatcTCTAGAATGAACAGCACATGTATTGAAG-3' (SEQ.ID.NO.: 125; sense)

15 5'-ctagGGTACCCGCTCAAGGACCTCTAATTCCATAG-3' (SEQ.ID.NO.: 126; antisense).

Nucleotides in lower caps are included as spacers in the restriction sites between the G protein and TDAG8. The sense and anti-sense primers included the restriction sites for XbaI and KpnI, respectively.

PCR was then utilized to secure the respective receptor sequences for fusion within  
20 the Gs $\alpha$  universal vector disclosed above, using the following protocol for each: 100ng cDNA for TDAG8 was added to separate tubes containing 2ul of each primer (sense and anti-sense), 3uL of 10mM dNTPs, 10uL of 10XTaqPlus™ Precision buffer, 1uL of TaqPlus™ Precision polymerase (Stratagene: #600211), and 80uL of water. Reaction temperatures and cycle times for TDAG8 were as follows: the initial denaturing step was done at 94°C for five minutes, and

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a cycle of 94°C for 30 seconds; 55°C for 30 seconds; 72°C for two minutes. A final extension time was done at 72°C for ten minutes. PCR product for was run on a 1% agarose gel and then purified (data not shown). The purified product was digested with XbaI and KpnI (New England Biolabs) and the desired inserts purified and ligated into the Gs universal  
5 vector at the respective restriction site. The positive clones was isolated following transformation and determined by restriction enzyme digest; expression using 293 cells was accomplished following the protocol set forth *infra*. Each positive clone for TDAG8:Gs - Fusion Protein was sequenced to verify correctness.

GPCR Fusion Proteins comprising non-endogenous, constitutively activated  
10 TDAG8(I225K) were analyzed as above and verified for constitutive activation.

An H9(F236K)-Gsa Fusion Protein construct was made as follows: primers were designed as follows:

5'-TTAgatcGGGGCCACCCTAGCGGT-3' (SEQ.ID.NO.: 145; sense)

5'-ggtaccCCCACAGCCATTCATCAGGATC-3' (SEQ.ID.NO.: 146; antisense).

15 Nucleotides in lower caps are included as spacers in the restriction sites between the G protein and H9. The sense and anti-sense primers included the restriction sites for EcoRV and KpnI, respectively such that spacers (attributed to the restriction sites) exists between the G protein and H9.

PCR was then utilized to secure the respective receptor sequences for fusion within  
20 the Gsa universal vector disclosed above, using the following protocol for each: 80ng cDNA for H9 was added to separate tubes containing 100ng of each primer (sense and anti-sense), and 45uL of PCR Supermix™ (Gibco-Brl, LifeTech) (50ul total reaction volume). Reaction temperatures and cycle times for H9 were as follows: the initial denaturing step was done at 94°C for one, and a cycle of 94°C for 30 seconds; 55°C for 30 seconds; 72°C for two

minutes. A final extension time was done at 72°C for seven minutes. PCR product for was run on a 1% agarose gel and then purified (data not shown). The purified product was cloned into pCRII-TOPO™ System followed by identification of positive clones. Positive clones were isolated, digested with EcoRV and KpnI (New England Biolabs) and the desired inserts  
 5 were isolated, purified and ligated into the Gs universal vector at the respective restriction site. The positive clones was isolated following transformation and determined by restriction enzyme digest; expression using 293 cells was accomplished following the protocol set forth *infra*. Each positive clone for H9(F236K):Gs - Fusion Protein was sequenced to verify correctness. Membranes were frozen (-80°C) until utilized.

10 To ascertain the ability of measuring a cAMP response mediated by the Gs protein (even though H9 couples with Gz), the following cAMP membrane assay was utilized, based upon an NEN Adenyl Cyclase Activation Flahplate™ Assay kit (96 well format). "Binding Buffer" consisted of 10mM HEPES, 100mM NaCl and 10mM MgCl (ph 7.4). "Regeneration Buffer" was prepared in Binding Buffer and consisted of 20mM phosphocreatine, 20U  
 15 creatine phosphokinase, 20uM GTP, 0.2mM ATP, and 0.6mM IBMX. "cAMP Standards" were prepared in Binding Buffer as follows:

		cAMP Stock (5,000 pmol/ml in 2ml H <sub>2</sub> O) in ul	Added to indicted amount of Binding Buffer	Final Assay Concentration (50ul into 100ul) to achieve indicated pmol/well
20	A	250	1ml	50
	B	500 of A	500ul	25
	C	500 of B	500ul	12.5
	D	500 of C	750ul	5.0
	E	500 of D	500ul	2.5
25	F	500 of E	500ul	1.25
	G	500 of F	750ul	0.5

Frozen membranes (both pCMV as control and the non-endogenous H(-Gs Fusion Protein) were thawed (on ice at room temperature until in solution). Membranes were

homogenized with a polytron until in suspension (2 x 15 seconds). Membrane protein concentration was determined using the Bradford Assay Protocol (*see infra*). Membrane concentration was diluted to 0.5mg/ml in Regeneration Buffer (final assay concentration - 25ug/well). Thereafter, 50ul of Binding Buffer was added to each well. For control, 50ul/well of cAMP standard was added to wells 11 and 12 A-G, with Binding Buffer alone to 12H (on the 96-well format). Thereafter, 50ul/well of protein was added to the wells and incubated at room temperature (on shaker) for 60min. 100ul [<sup>125</sup>I]cAMP in Detection Buffer (*see infra*) was added to each well (final - 50ul [<sup>125</sup>I]cAMP into 11ml Detection Buffer). These were incubated for 2hrs at room temperature. Plates were aspirated with an 8 channel manifold and sealed with plate covers. Results (pmoles cAMP bound) were read in a Wallac™ 1450 on "prot #15). Results are presented in Figure 3.

The results presented in Figure 3 indicate that the Gs coupled fusion was able to "drive" the cyclase reaction such that measurement of the constitutive activation of H9(F236K) was viable. Based upon these results, the direct identification of candidate compounds that are inverse agonists, agonists and partial agonists is possible using a cyclase-based assay.

#### Example 6

##### Protocol: Direct Identification of Inverse Agonists and Agonists Using [<sup>35</sup>S]GTPγS

Although we have utilized endogenous, constitutively active GPCRs for the direct identification of candidate compounds as, *e.g.*, inverse agonists, for reasons that are not altogether understood, intra-assay variation can become exacerbated. Preferably, then, a GPCR Fusion Protein, as disclosed above, is also utilized with a non-endogenous, constitutively activated GPCR. We have determined that when such a protein is used, intra-assay variation appears to be substantially stabilized, whereby an effective signal-to-noise ratio is obtained. This has the beneficial result of allowing for a more robust identification



of candidate compounds. Thus, it is preferred that for direct identification, a GPCR Fusion Protein be used and that when utilized, the following assay protocols be utilized.

### **Membrane Preparation**

Membranes comprising the non-endogenous, constitutively active orphan GPCR Fusion Protein of interest and for use in the direct identification of candidate compounds as inverse agonists, agonists or partial agonists are preferably prepared as follows:

#### **a. Materials**

"Membrane Scrape Buffer" is comprised of 20mM HEPES and 10mM EDTA, pH 7.4;

"Membrane Wash Buffer" is comprised of 20 mM HEPES and 0.1 mM EDTA, pH 7.4;

10 "Binding Buffer" is comprised of 20mM HEPES, 100 mM NaCl, and 10 mM MgCl<sub>2</sub>, pH 7.4

#### **b. Procedure**

All materials are kept on ice throughout the procedure. Firstly, the media is aspirated from a confluent monolayer of cells, followed by rinse with 10ml cold PBS, followed by aspiration. Thereafter, 5ml of Membrane Scrape Buffer is added to scrape cells; this is followed by transfer of cellular extract into 50ml centrifuge tubes (centrifuged at 20,000 rpm for 17 minutes at 4°C). Thereafter, the supernatant is aspirated and the pellet is resuspended in 30ml Membrane Wash Buffer followed by centrifuge at 20,000 rpm for 17 minutes at 4°C. The supernatant is then aspirated and the pellet resuspended in Binding Buffer. This is then homogenized using a Brinkman polytron™ homogenizer (15-20 second bursts until the all material is in suspension). This is referred to herein as "Membrane Protein".

### **Bradford Protein Assay**

Following the homogenization, protein concentration of the membranes is determined using the Bradford Protein Assay (protein can be diluted to about 1.5mg/ml, aliquoted and

frozen (-80°C) for later use; when frozen, protocol for use is as follows: on the day of the assay, frozen Membrane Protein is thawed at room temperature, followed by vortex and then homogenized with a polytron at about 12 x 1,000 rpm for about 5-10 seconds; it is noted that for multiple preparations, the homogenizer should be thoroughly cleaned between  
5 homogenization of different preparations).

**a. Materials**

Binding Buffer (as per above); Bradford Dye Reagent; Bradford Protein Standard are utilized, following manufacturer instructions (Biorad, cat. no. 500-0006).

**b. Procedure**

10 Duplicate tubes are prepared, one including the membrane, and one as a control "blank". Each contained 800ul Binding Buffer. Thereafter, 10ul of Bradford Protein Standard (1mg/ml) is added to each tube, and 10ul of membrane Protein is then added to just one tube (not the blank). Thereafter, 200ul of Bradford Dye Reagent is added to each tube, followed by vortex of each. After five (5) minutes, the tubes were re-vortexed and the material therein  
15 is transferred to cuvettes. The cuvettes are then read using a CECIL 3041 spectrophotometer, at wavelength 595.

**Direct Identification Assay**

**a. Materials**

GDP Buffer consists of 37.5 ml Binding Buffer and 2mg GDP (Sigma, cat. no. G-  
20 7127), followed by a series of dilutions in Binding Buffer to obtain 0.2 uM GDP (final concentration of GDP in each well was 0.1 uM GDP); each well comprising a candidate compound, has a final volume of 200ul consisting of 100ul GDP Buffer (final concentration, 0.1uM GDP), 50ul Membrane Protein in Binding Buffer, and 50ul [<sup>35</sup>S]GTPγS (0.6 nM) in

Binding Buffer (2.5 ul [ $^{35}$ S]GTP $\gamma$ S per 10ml Binding Buffer).

**b. Procedure**

Candidate compounds are preferably screened using a 96-well plate format (these can be frozen at -80°C). Membrane Protein (or membranes with expression vector excluding the GPCR Fusion Protein, as control), are homogenized briefly until in suspension. Protein concentration is then determined using the Bradford Protein Assay set forth above. Membrane Protein (and control) is then diluted to 0.25mg/ml in Binding Buffer (final assay concentration, 12.5ug/well). Thereafter, 100 ul GDP Buffer is added to each well of a Wallac Scintistrip™ (Wallac). A 5ul pin-tool is then used to transfer 5 ul of a candidate compound into such well (*i.e.*, 5ul in total assay volume of 200 ul is a 1:40 ratio such that the final screening concentration of the candidate compound is 10uM). Again, to avoid contamination, after each transfer step the pin tool should be rinsed in three reservoirs comprising water (1X), ethanol (1X) and water (2X) – excess liquid should be shaken from the tool after each rinse and dried with paper and kimwipes. Thereafter, 50 ul of Membrane Protein is added to each well (a control well comprising membranes without the GPCR Fusion Protein is also utilized), and pre-incubated for 5-10 minutes at room temperature. Thereafter, 50 ul of [ $^{35}$ S]GTP $\gamma$ S (0.6 nM) in Binding Buffer is added to each well, followed by incubation on a shaker for 60 minutes at room temperature (again, in this example, plates were covered with foil). The assay is then stopped by spinning of the plates at 4000 RPM for 15 minutes at 22°C. The plates are then aspirated with an 8 channel manifold and sealed with plate covers. The plates are then read on a Wallac 1450 using setting "Prot. #37" (as per manufacturer instructions).

**Example 7**

**Protocol: Confirmation Assay**

Using an independent assay approach to provide confirmation of a directly identified

candidate compound as set forth above, it is preferred that a confirmation assay then be utilized. In this case, the preferred confirmation assay is a cyclase-based assay.

A modified Flash Plate™ Adenylyl Cyclase kit (New England Nuclear; Cat. No. SMP004A) is preferably utilized for confirmation of candidate compounds directly identified  
5 as inverse agonists and agonists to non-endogenous, constitutively activated orphan GPCRs in accordance with the following protocol.

Transfected cells are harvested approximately three days after transfection. Membranes are prepared by homogenization of suspended cells in buffer containing 20mM HEPES, pH 7.4 and 10mM MgCl<sub>2</sub>. Homogenization is performed on ice using a Brinkman  
10 Polytron™ for approximately 10 seconds. The resulting homogenate is centrifuged at 49,000 X g for 15 minutes at 4°C. The resulting pellet is then resuspended in buffer containing 20mM HEPES, pH 7.4 and 0.1 mM EDTA, homogenized for 10 seconds, followed by centrifugation at 49,000 X g for 15 minutes at 4°C. The resulting pellet can be stored at -80°C until utilized. On the day of direct identification screening, the membrane pellet is  
15 slowly thawed at room temperature, resuspended in buffer containing 20mM HEPES, pH 7.4 and 10mM MgCL2, to yield a final protein concentration of 0.60mg/ml (the resuspended membranes are placed on ice until use).

cAMP standards and Detection Buffer (comprising 2 μCi of tracer [<sup>125</sup>I] cAMP (100 μl) to 11 ml Detection Buffer) are prepared and maintained in accordance with the  
20 manufacturer's instructions. Assay Buffer is prepared fresh for screening and contained 20mM HEPES, pH 7.4, 10mM MgCl<sub>2</sub>, 20mM phosphocreatine (Sigma), 0.1 units/ml creatine phosphokinase (Sigma), 50 μM GTP (Sigma), and 0.2 mM ATP (Sigma); Assay Buffer can be stored on ice until utilized.

Candidate compounds identified as per above (if frozen, thawed at room temperature) are added, preferably, to 96-well plate wells ( $3\mu\text{l}$ /well;  $12\mu\text{M}$  final assay concentration), together with  $40\mu\text{l}$  Membrane Protein ( $30\mu\text{g}$ /well) and  $50\mu\text{l}$  of Assay Buffer. This admixture is then incubated for 30 minutes at room temperature, with gentle shaking.

5        Following the incubation,  $100\mu\text{l}$  of Detection Buffer is added to each well, followed by incubation for 2-24 hours. Plates are then counted in a Wallac MicroBeta™ plate reader using "Prot. #31" (as per manufacturer instructions).

It is intended that each of the patents, applications, and printed publications mentioned in this patent document be hereby incorporated by reference in their entirety.

10        As those skilled in the art will appreciate, numerous changes and modifications may be made to the preferred embodiments of the invention without departing from the spirit of the invention. It is intended that all such variations fall within the scope of the invention.

Although a variety of expression vectors are available to those in the art, for purposes of utilization for both the endogenous and non-endogenous human GPCRs, it is most preferred that the vector utilized be pCMV. This vector was deposited with the  
15        American Type Culture Collection (ATCC) on October 13, 1998 (10801 University Blvd., Manassas, VA 20110-2209 USA) under the provisions of the Budapest Treaty for the International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure. The DNA was tested by the ATCC and determined to be. The ATCC has  
20        assigned the following deposit number to pCMV: ATCC #203351.

## CLAIMS

What is claimed is:

1. A cDNA encoding a non-endogenous, constitutively activated version of a human G protein-coupled receptor comprising hARE-3(F313K).
- 5 2. A non-endogenous version of a human G protein-coupled receptor encoded by the cDNA of claim 1.
3. A Plasmid comprising a Vector and the cDNA of claim 1.
4. A Host Cell comprising the Plasmid of claim 3.
5. A cDNA encoding a non-endogenous, constitutively activated version of a human
- 10 G protein-coupled receptor comprising hARE-4(V233K)
6. A non-endogenous version of a human G protein-coupled receptor encoded by the cDNA of claim 5.
7. A Plasmid comprising a Vector and the cDNA of claim 5.
8. A Host Cell comprising the Plasmid of claim 7.
- 15 9. A cDNA encoding a non-endogenous, constitutively activated version of a human G protein-coupled receptor comprising hARE-5(A240K).
10. A non-endogenous version of a human G protein-coupled receptor encoded by the cDNA of claim 9.
11. A Plasmid comprising a Vector and the cDNA of claim 5.
- 20 12. A Host Cell comprising the Plasmid of claim 11.
13. A cDNA encoding a non-endogenous, constitutively activated version of a human G protein-coupled receptor comprising hGPCR14(L257K).

14. A non-endogenous version of a human G protein-coupled receptor encoded by the cDNA of claim 13.
15. A Plasmid comprising a Vector and the cDNA of claim 13.
- 5 16. A Host Cell comprising the Plasmid of claim 15.
17. A cDNA encoding a non-endogenous, constitutively activated version of a human G protein-coupled receptor comprising hGPCR27(C283K).
18. A non-endogenous version of a human G protein-coupled receptor encoded by the cDNA of claim 17.
- 10 19. A Plasmid comprising a Vector and the cDNA of claim 17.
20. A Host Cell comprising the Plasmid of claim 19.
21. A cDNA encoding a non-endogenous, constitutively activated version of a human G protein-coupled receptor comprising hARE-1(E232K).
22. A non-endogenous version of a human G protein-coupled receptor encoded by the cDNA of claim 21.
- 15 23. A Plasmid comprising a Vector and the cDNA of claim 21.
24. A Host Cell comprising the Plasmid of claim 23.
25. A cDNA encoding a non-endogenous, constitutively activated version of a human G protein-coupled receptor comprising hARE-2(G285K).
- 20 26. A non-endogenous version of a human G protein-coupled receptor encoded by the cDNA of claim 25.
27. A Plasmid comprising a Vector and the cDNA of claim 25.
28. A Host Cell comprising the Plasmid of claim 27.

29. A cDNA encoding a non-endogenous, constitutively activated version of a human G protein-coupled receptor comprising hPPR1(L239K).
30. A non-endogenous version of a human G protein-coupled receptor encoded by the cDNA of claim 29.
- 5 31. A Plasmid comprising a Vector and the cDNA of claim 29.
32. A Host Cell comprising the Plasmid of claim 31.
33. A cDNA encoding a non-endogenous, constitutively activated version of a human G protein-coupled receptor comprising hG2A(K232A).
34. A non-endogenous version of a human G protein-coupled receptor encoded by the cDNA of claim 33.
- 10 35. A Plasmid comprising a Vector and the cDNA of claim 33.
36. A Host Cell comprising the Plasmid of claim 35.
37. A cDNA encoding a non-endogenous, constitutively activated version of a human G protein-coupled receptor comprising hRUP3(L224K).
- 15 38. A non-endogenous version of a human G protein-coupled receptor encoded by the cDNA of claim 37.
39. A Plasmid comprising a Vector and the cDNA of claim 37.
40. A Host Cell comprising the Plasmid of claim 39.
41. A cDNA encoding a non-endogenous, constitutively activated version of a human G protein-coupled receptor comprising hRUP5(A236K).
- 20 42. A non-endogenous version of a human G protein-coupled receptor encoded by the cDNA of claim 41.
43. A Plasmid comprising a Vector and the cDNA of claim 41.



44. A Host Cell comprising the Plasmid of claim 42.
45. A cDNA encoding a non-endogenous, constitutively activated version of a human  
G protein-coupled receptor comprising hRUP6(N267K)
46. A non-endogenous version of a human G protein-coupled receptor encoded by the  
5 cDNA of claim 45.
47. A Plasmid comprising a Vector and the cDNA of claim 45.
48. A Host Cell comprising the Plasmid of claim 47.
49. A cDNA encoding a non-endogenous, constitutively activated version of a human  
G protein-coupled receptor comprising hRUP7(A302K).
- 10 50. A non-endogenous version of a human G protein-coupled receptor encoded by the  
cDNA of claim 49.
51. A Plasmid comprising a Vector and the cDNA of claim 49.
52. A Host Cell comprising the Plasmid of claim 51.
53. A cDNA encoding a non-endogenous, constitutively activated version of a human  
15 G protein-coupled receptor comprising hCHN4(V236K).
54. A non-endogenous version of a human G protein-coupled receptor encoded by the  
cDNA of claim 53.
55. A Plasmid comprising a Vector and the cDNA of claim 53.
56. A Host Cell comprising the Plasmid of claim 55.
- 20 57. A cDNA encoding a non-endogenous, constitutively activated version of a human  
G protein-coupled receptor comprising hMC4(A244K).
58. A non-endogenous version of a human G protein-coupled receptor encoded by the  
cDNA of claim 57.

59. A Plasmid comprising a Vector and the cDNA of claim 57.
60. A Host Cell comprising the Plasmid of claim 60.
61. A cDNA encoding a non-endogenous, constitutively activated version of a human  
G protein-coupled receptor comprising hCHN3(S284K).
- 5 62. A non-endogenous version of a human G protein-coupled receptor encoded by the  
cDNA of claim 61.
63. A Plasmid comprising a Vector and the cDNA of claim 61.
64. A Host Cell comprising the Plasmid of claim 63.
65. A cDNA encoding a non-endogenous, constitutively activated version of a human  
10 G protein-coupled receptor comprising hCHN6(L352K).
66. A non-endogenous version of a human G protein-coupled receptor encoded by the  
cDNA of claim 65.
67. A Plasmid comprising a Vector and the cDNA of claim 65.
68. A Host Cell comprising the Plasmid of claim 67.
- 15 69. A cDNA encoding a non-endogenous, constitutively activated version of a human  
G protein-coupled receptor comprising hCHN8(N235K).
70. A non-endogenous version of a human G protein-coupled receptor encoded by the  
cDNA of claim 69.
71. A Plasmid comprising a Vector and the cDNA of claim 69.
- 20 72. A Host Cell comprising the Plasmid of claim 71.
73. A cDNA encoding a non-endogenous, constitutively activated version of a human  
G protein-coupled receptor comprising hH9(F236K).
74. A non-endogenous version of a human G protein-coupled receptor encoded by the

cDNA of claim 73.

75. A Plasmid comprising a Vector and the cDNA of claim 73.

76. A Host Cell comprising the Plasmid of claim 74.

77. A cDNA encoding a non-endogenous, constitutively activated version of a human

5 G protein-coupled AT1 receptor selected from the group consisting of:

hAT1(F239K); hAT1(N111A); hAT1(AT2K255IC3); and hAT1(A243+).

78. A non-endogenous version of a human G protein-coupled receptor encoded by a  
cDNA of claim 77.

79. A Plasmid comprising a Vector and the cDNA of claim 77.

10 80. A Host Cell comprising the Plasmid of claim 79.

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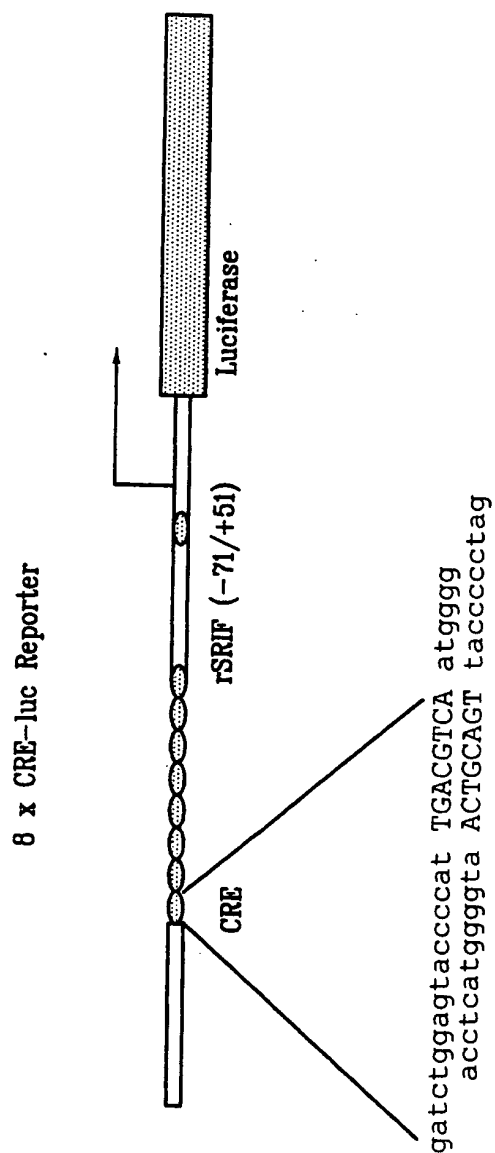


FIG. 1

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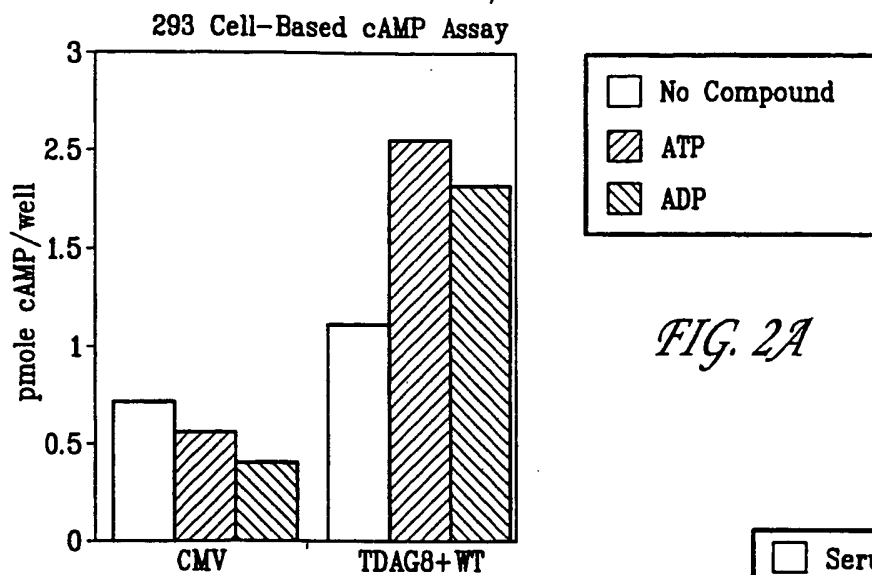


FIG. 2A

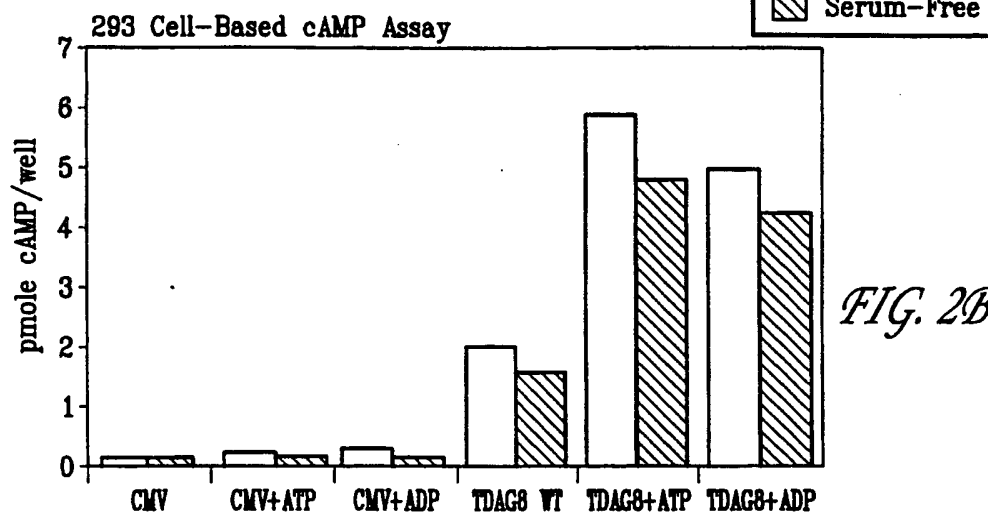


FIG. 2B

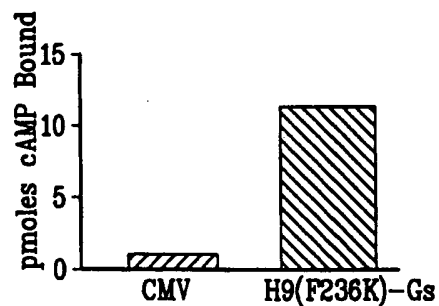


FIG. 3

- 1 -

## SEQUENCE LISTING

## (1) GENERAL INFORMATION:

- 5 (i) APPLICANT: Behan, Dominic P.  
Lehmann-Bruinsma, Karin  
Chalmers, Derek T.  
Lowitz, Kevin P.  
Lin, I-Lin  
10 Dang, Huong T.  
Chen, Ruoping  
Liaw, Chen W.  
Gore, Martin J.  
White, Carol
- 15 (ii) TITLE OF INVENTION: Non-Endogenous, Constitutively Activated Human G  
Protein-Coupled Receptors
- (iii) NUMBER OF SEQUENCES: 146
- 20 (iv) CORRESPONDENCE ADDRESS:  
(A) ADDRESSEE: Arena Pharmaceuticals, Inc.  
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(E) COUNTRY: USA  
(F) ZIP: 92121
- 25 (v) COMPUTER READABLE FORM:  
(A) MEDIUM TYPE: Floppy disk  
(B) COMPUTER: IBM PC compatible  
(C) OPERATING SYSTEM: PC-DOS/MS-DOS  
(D) SOFTWARE: PatentIn Release #1.0, Version #1.30
- 30 (vi) CURRENT APPLICATION DATA:  
(A) APPLICATION NUMBER: US  
(B) FILING DATE:  
(C) CLASSIFICATION:
- 35 (viii) ATTORNEY/AGENT INFORMATION:  
(A) NAME: Burgoon, Richard P.  
(B) REGISTRATION NUMBER: 34,787
- (ix) TELECOMMUNICATION INFORMATION:  
(A) TELEPHONE: (858)453-7200  
(B) TELEFAX: (858)453-7210
- 40 (2) INFORMATION FOR SEQ ID NO:1:
- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 1260 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single

- 2 -

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

ATGGTCTTCT CGGCAGTGTT GACTGCGTTC CATACCGGGA CATCCAACAC AACATTTGTC 60  
5 GTGTATGAAA ACACCTACAT GAATATTACA CTCCCTCCAC CATTCCAGCA TCCTGACCTC 120  
AGTCCATTGC TTAGATATAG TTTTGAAACC ATGGCTCCCA CTGGTTTGAG TTCCTTGACC 180  
GTGAATAGTA CAGCTGTGCC CACAACACCA GCAGCATTTA AGAGCCTAAA CTGCTCTCTT 240  
CAGATCACCC TTTCTGCTAT AATGATATTC ATTCTGTTTG TGTCTTTTCT TGGGAACCTG 300  
GTTGTTTGCC TCATGGTTTA CCAAAAAGCT GCCATGAGGT CTGCAATTAA CATCCTCCTT 360  
10 GCCAGCCTAG CTTTTGCAGA CATGTTGCTT GCAGTGCTGA ACATGCCCTT TGCCCTGGTA 420  
ACTATTCTTA CTACCCGATG GATTTTTGGG AAATCTTCT GTAGGGTATC TGCTATGTTT 480  
TTCTGGTTAT TTGTGATAGA AGGAGTAGCC ATCCTGCTCA TCATTAGCAT AGATAGGTTC 540  
CTTATTATAG TCCAGAGGCA GGATAAGCTA AAGCCATATA GAGCTAAGGT TCTGATTGCA 600  
GTTTCTTGGG CAACTTCCTT TTGTGTAGCT TTTCTTTAG CCGTAGGAAA CCCCAGCTG 660  
15 CAGATACCTT CCCGAGCTCC CCAGTGTGTG TTTGGGTACA CAACCAATCC AGGCTACCAG 720  
GCTTATGTGA TTTTGATTTT TCTCATTTCT TTCTTCATAC CTTCTCTGGT AATACTGTAC 780  
TCATTTATGG GCATACTCAA CACCCTTCGG CACAATGCCT TGAGGATCCA TAGCTACCTT 840  
GAAGGTATAT GCCTCAGCCA GGCCAGCAAA CTGGGTCTCA TGAGTCTGCA GAGACCTTTC 900  
CAGATGAGCA TTGACATGGG CTTTAAACA CGTGCCTTCA CCACTATTTT GATTCTCTTT 960  
20 GCTGTCTTCA TTGTCTGCTG GGCCCCATTC ACCACTTACA GCCTTGTTGC AACATTCAGT 1020  
AAGCACTTTT ACTATCAGCA CAACTTTTTT GAGATTAGCA CCTGGCTACT GTGGCTCTGC 1080  
TACCTCAAGT CTGCATTGAA TCCGCTGATC TACTACTGGA GGATTAAGAA ATTCCATGAT 1140  
GCTTGCTTGG ACATGATGCC TAAGTCCTTC AAGTTTTTGC CGCAGCTCCC TGGTCACACA 1200  
AAGCGACGGA TACGTCCTAG TGCTGTCTAT GTGTGTGGGG AACATCGGAC GGTGGTGTGA 1260

25 (3) INFORMATION FOR SEQ ID NO:2:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 419 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

30

- 3 -

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Met Val Phe Ser Ala Val Leu Thr Ala Phe His Thr Gly Thr Ser Asn  
 1 5 10 15  
 5 Thr Thr Phe Val Val Tyr Glu Asn Thr Tyr Met Asn Ile Thr Leu Pro  
 20 25 30  
 Pro Pro Phe Gln His Pro Asp Leu Ser Pro Leu Leu Arg Tyr Ser Phe  
 35 40 45  
 10 Glu Thr Met Ala Pro Thr Gly Leu Ser Ser Leu Thr Val Asn Ser Thr  
 50 55 60  
 Ala Val Pro Thr Thr Pro Ala Ala Phe Lys Ser Leu Asn Leu Pro Leu  
 65 70 75 80  
 Gln Ile Thr Leu Ser Ala Ile Met Ile Phe Ile Leu Phe Val Ser Phe  
 85 90 95  
 15 Leu Gly Asn Leu Val Val Cys Leu Met Val Tyr Gln Lys Ala Ala Met  
 100 105 110  
 Arg Ser Ala Ile Asn Ile Leu Leu Ala Ser Leu Ala Phe Ala Asp Met  
 115 120 125  
 20 Leu Leu Ala Val Leu Asn Met Pro Phe Ala Leu Val Thr Ile Leu Thr  
 130 135 140  
 Thr Arg Trp Ile Phe Gly Lys Phe Phe Cys Arg Val Ser Ala Met Phe  
 145 150 155 160  
 Phe Trp Leu Phe Val Ile Glu Gly Val Ala Ile Leu Leu Ile Ile Ser  
 165 170 175  
 25 Ile Asp Arg Phe Leu Ile Ile Val Gln Arg Gln Asp Lys Leu Asn Pro  
 180 185 190  
 Tyr Arg Ala Lys Val Leu Ile Ala Val Ser Trp Ala Thr Ser Phe Cys  
 195 200 205  
 30 Val Ala Phe Pro Leu Ala Val Gly Asn Pro Asp Leu Gln Ile Pro Ser  
 210 215 220  
 Arg Ala Pro Gln Cys Val Phe Gly Tyr Thr Thr Asn Pro Gly Tyr Gln  
 225 230 235 240  
 Ala Tyr Val Ile Leu Ile Ser Leu Ile Ser Phe Phe Ile Pro Phe Leu  
 245 250 255  
 35 Val Ile Leu Tyr Ser Phe Met Gly Ile Leu Asn Thr Leu Arg His Asn  
 260 265 270



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Ala Leu Arg Ile His Ser Tyr Pro Glu Gly Ile Cys Leu Ser Gln Ala  
 275 280 285

Ser Lys Leu Gly Leu Met Ser Leu Gln Arg Pro Phe Gln Met Ser Ile  
 290 295 300

5 Asp Met Gly Phe Lys Thr Arg Ala Phe Thr Thr Ile Leu Ile Leu Phe  
 305 310 315 320

Ala Val Phe Ile Val Cys Trp Ala Pro Phe Thr Thr Tyr Ser Leu Val  
 325 330 335

10 Ala Thr Phe Ser Lys His Phe Tyr Tyr Gln His Asn Phe Phe Glu Ile  
 340 345 350

Ser Thr Trp Leu Leu Trp Leu Cys Tyr Leu Lys Ser Ala Leu Asn Pro  
 355 360 365

Leu Ile Tyr Tyr Trp Arg Ile Lys Lys Phe His Asp Ala Cys Leu Asp  
 370 375 380

15 Met Met Pro Lys Ser Phe Lys Phe Leu Pro Gln Leu Pro Gly His Thr  
 385 390 395 400

Lys Arg Arg Ile Arg Pro Ser Ala Val Tyr Val Cys Gly Glu His Arg  
 405 410 415

20 Thr Val Val

## (4) INFORMATION FOR SEQ ID NO:3:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 1119 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

ATGTTAGCCA ACAGCTCCTC AACCAACAGT TCTGTTCTCC CGTGTCTCTGA CTACCGACCT 60

30 ACCCACC GCC TGGCTTGGT GGTCTACAGC TTGGTGCTGG CTGCCGGGCT CCCCCCAAC 120

GCGCTAGCCC TCTGGGTCTT CCTGCGCGCG CTGCGCGTGC ACTCGGTGGT GAGCGTGATC 180

ATGTGTAACC TGGCGGCCAG CGACCTGCTC TTCACCCTCT CGCTGCCCCG TCGTCTCTCC 240

TACTACGCAC TGCACCACTG GCCCTTCCCC GACCTCCTGT GCCAGACGAC GGGCGCCATC 300

TTCCAGATGA ACATGTACGG CAGCTGCATC TTCCTGATGC TCATCAACGT GGACCGCTAC 360

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GCCGCCATCG TGCACCCGCT GCGACTGCGC CACCTGCGGC GGCCCCGCGT GGCGCGGCTG 420  
 CTCTGCCTGG GCGTGTGGGC GCTCATCCTG GTGTTTGCCG TGCCCGCCGC CCGCGTGCAC 480  
 AGGCCCTCGC GTTGCCGCTA CCGGGACCTC GAGGTGCGCC TATGCTTCGA GAGCTTCAGC 540  
 GACGAGCTGT GGAAAGGCAG GCTGCTGCCC CTCGTGCTGC TGGCCGAGGC GCTGGGCTTC 600  
 5 CTGCTGCCCC TGGCGGCGGT GGTCTACTCG TCGGGCCGAG TCTTCTGGAC GCTGGCGCGC 660  
 CCCGACGCCA CGCAGAGCCA GCGGCGGCGG AAGACCGTGC GCCTCCTGCT GGCTAACCTC 720  
 GTCATCTTCC TGCTGTGCTT CGTGCCCTAC AACAGCACGC TGGCGGTCTA CGGGCTGCTG 780  
 CGGAGCAAGC TGGTGGCGGC CAGCGTGCCT GCCCGCGATC GCGTGCGCGG GGTGCTGATG 840  
 GTGATGGTGC TGCTGGCCGG CGCCAACCTG GTGCTGGACC CGCTGGTGTA CTACTTTAGC 900  
 10 GCCGAGGGCT TCCGCAACAC CCTGCGCGGC CTGGGCACTC CGCACCAGGC CAGGACCTCG 960  
 GCCACCAACG GGACGCGGGC GCGCTCGCG CAATCCGAAA GGTCCGCCGT CACCACCGAC 1020  
 GCCACCAGGC CGGATGCCGC CAGTCAGGGG CTGCTCCGAC CCTCCGACTC CCACTCTCTG 1080  
 TCTTCCTTCA CACAGTGTC CCAGGATCC GCCCTCTGA 1119

(5) INFORMATION FOR SEQ ID NO:4:

- 15 (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 372 amino acids  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS:  
 (D) TOPOLOGY: not relevant.

20 (ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

Met Leu Ala Asn Ser Ser Ser Thr Asn Ser Ser Val Leu Pro Cys Pro  
 1 5 10 15  
 Asp Tyr Arg Pro Thr His Arg Leu His Leu Val Val Tyr Ser Leu Val  
 25 20 25 30  
 Leu Ala Ala Gly Leu Pro Leu Asn Ala Leu Ala Leu Trp Val Phe Leu  
 35 40 45  
 Arg Ala Leu Arg Val His Ser Val Val Ser Val Tyr Met Cys Asn Leu  
 50 55 60  
 30 Ala Ala Ser Asp Leu Leu Phe Thr Leu Ser Leu Pro Val Arg Leu Ser  
 65 70 75 80  
 Tyr Tyr Ala Leu His His Trp Pro Phe Pro Asp Leu Leu Cys Gln Thr

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	85	90	95
	Thr Gly Ala Ile Phe Gln Met Asn Met Tyr Gly Ser Cys Ile Phe Leu 100 105 110		
5	Met Leu Ile Asn Val Asp Arg Tyr Ala Ala Ile Val His Pro Leu Arg 115 120 125		
	Leu Arg His Leu Arg Arg Pro Arg Val Ala Arg Leu Leu Cys Leu Gly 130 135 140		
	Val Trp Ala Leu Ile Leu Val Phe Ala Val Pro Ala Ala Arg Val His 145 150 155 160		
10	Arg Pro Ser Arg Cys Arg Tyr Arg Asp Leu Glu Val Arg Leu Cys Phe 165 170 175		
	Glu Ser Phe Ser Asp Glu Leu Trp Lys Gly Arg Leu Leu Pro Leu Val 180 185 190		
15	Leu Leu Ala Glu Ala Leu Gly Phe Leu Leu Pro Leu Ala Ala Val Val 195 200 205		
	Tyr Ser Ser Gly Arg Val Phe Trp Thr Leu Ala Arg Pro Asp Ala Thr 210 215 220		
	Gln Ser Gln Arg Arg Arg Lys Thr Val Arg Leu Leu Leu Ala Asn Leu 225 230 235 240		
20	Val Ile Phe Leu Leu Cys Phe Val Pro Tyr Asn Ser Thr Leu Ala Val 245 250 255		
	Tyr Gly Leu Leu Arg Ser Lys Leu Val Ala Ala Ser Val Pro Ala Arg 260 265 270		
25	Asp Arg Val Arg Gly Val Leu Met Val Met Val Leu Leu Ala Gly Ala 275 280 285		
	Asn Cys Val Leu Asp Pro Leu Val Tyr Tyr Phe Ser Ala Glu Gly Phe 290 295 300		
	Arg Asn Thr Leu Arg Gly Leu Gly Thr Pro His Arg Ala Arg Thr Ser 305 310 315 320		
30	Ala Thr Asn Gly Thr Arg Ala Ala Leu Ala Gln Ser Glu Arg Ser Ala 325 330 335		
	Val Thr Thr Asp Ala Thr Arg Pro Asp Ala Ala Ser Gln Gly Leu Leu 340 345 350		
35	Arg Pro Ser Asp Ser His Ser Leu Ser Ser Phe Thr Gln Cys Pro Gln 355 360 365		
	Asp Ser Ala Leu 370		

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## (6) INFORMATION FOR SEQ ID NO:5:

## (i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 1107 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: DNA (genomic)

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

ATGGCCAACT CCACAGGGCT GAACGCCTCA GAAGTCGCAG GCTCGTTGGG GTTGATCCTG 60  
10 GCAGCTGTCTG TGGAGGTGGG GGCAGTCTG GGCACCGGCG CGCTGCTGGT CGTGGTGCTG 120  
CGCAGCGCCG GACTGCGCGA CGCGCTCTAC CTGGCGCACC TGTGCGTCGT GGACCTGCTG 180  
GCGGCCGCGCT CCATCATGCC GCTGGGCCTG CTGGCCGCAC CGCCGCCCGG GCTGGGCGCG 240  
GTGCGCCTGG GCGCCGCGCC ATGCCGCGCC GCTCGCTTCC TCTCCGCCGC TCTGCTGCCG 300  
GCCTGCACGC TCGGGGTGGC CGCACTTGGC CTGGCAGCT ACCGCCTCAT CGTGACCCG 360  
15 CTGCGGCCAG GCTCGCGGCC GCCGCTGTG CTCGTGCTCA CCGCCGTGTG GGCCGCGGCG 420  
GGACTGCTGG GCGCGCTCTC CCTGCTCGGC CCGCCGCCCG CACCGCCCCG TGCTCTGCT 480  
CGCTGCTCGG TCCTGGCTGG GGGCCTCGGG CCCTTCCGGC CGCTCTGGGC CCTGCTGGCC 540  
TTCGCGCTGC CCGCCCTCCT GCTGCTCGGC GCCTACGGCG GCATCTTCGT GGTGGCGCGT 600  
CGCGCTGCCC TGAGGCCCCC ACGGCCGGCG CGCGGGTCCC GACTCCGCTC GGACTCTCTG 660  
20 GATAGCCGCC TTTCCATCTT GCCGCGCTC CGGCCTCGCC TGCCCGGGGG CAAGGCGGCC 720  
CTGGCCCCAG CGCTGGCCGT GGGCCAATTT GCAGCCTGCT GGCTGCCTTA TGGCTGCGCG 780  
TGCCTGGCGC CCGCAGCGCG GGCCGCGGAA GCCGAAGCGG CTGTCACCTG GGTCGCCTAC 840  
TCGGCCTTCG CGGCTCACC CTTCCTGTAC GGGCTGCTGC AGCGCCCCGT GCGCTTGGCA 900  
CTGGGCGGCC TCTCTCGCCG TGCACTGCCT GGACCTGTGC GGGCCTGCAC TCCGCAAGCC 960  
25 TGGCACCCGC GGGCACTCTT GCAATGCCTC CAGAGACCCC CAGAGGGCCC TGCCGTAGGC 1020  
CCTTCTGAGG CTCCAGAACA GACCCCGAG TTGGCAGGAG GCGGAGCCCC CGCATACCAG 1080  
GGGCCACCTG AGAGTTCTCT CTCCTGA 1107

## (7) INFORMATION FOR SEQ ID NO:6:

## (i) SEQUENCE CHARACTERISTICS:

- 30 (A) LENGTH: 368 amino acids

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- (B) TYPE: amino acid  
 (C) STRANDEDNESS:  
 (D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein

5 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

	Met	Ala	Asn	Ser	Thr	Gly	Leu	Asn	Ala	Ser	Glu	Val	Ala	Gly	Ser	Leu	
	1				5					10					15		
	Gly	Leu	Ile	Leu	Ala	Ala	Val	Val	Glu	Val	Gly	Ala	Leu	Leu	Gly	Asn	
			20						25					30			
10	Gly	Ala	Leu	Leu	Val	Val	Val	Leu	Arg	Thr	Pro	Gly	Leu	Arg	Asp	Ala	
		35						40					45				
	Leu	Tyr	Leu	Ala	His	Leu	Cys	Val	Val	Asp	Leu	Leu	Ala	Ala	Ala	Ser	
		50					55					60					
	Ile	Met	Pro	Leu	Gly	Leu	Leu	Ala	Ala	Pro	Pro	Pro	Gly	Leu	Gly	Arg	
15	65					70					75				80		
	Val	Arg	Leu	Gly	Pro	Ala	Pro	Cys	Arg	Ala	Ala	Arg	Phe	Leu	Ser	Ala	
					85					90					95		
	Ala	Leu	Leu	Pro	Ala	Cys	Thr	Leu	Gly	Val	Ala	Ala	Leu	Gly	Leu	Ala	
				100					105					110			
20	Arg	Tyr	Arg	Leu	Ile	Val	His	Pro	Leu	Arg	Pro	Gly	Ser	Arg	Pro	Pro	
			115					120					125				
	Pro	Val	Leu	Val	Leu	Thr	Ala	Val	Trp	Ala	Ala	Ala	Gly	Leu	Leu	Gly	
		130					135						140				
	Ala	Leu	Ser	Leu	Leu	Gly	Pro	Pro	Pro	Ala	Pro	Pro	Pro	Ala	Pro	Ala	
25	145					150					155				160		
	Arg	Cys	Ser	Val	Leu	Ala	Gly	Gly	Leu	Gly	Pro	Phe	Arg	Pro	Leu	Trp	
					165					170					175		
	Ala	Leu	Leu	Ala	Phe	Ala	Leu	Pro	Ala	Leu	Leu	Leu	Leu	Gly	Ala	Tyr	
				180					185					190			
30	Gly	Gly	Ile	Phe	Val	Val	Ala	Arg	Arg	Ala	Ala	Leu	Arg	Pro	Pro	Arg	
			195					200					205				
	Pro	Ala	Arg	Gly	Ser	Arg	Leu	Arg	Ser	Asp	Ser	Leu	Asp	Ser	Arg	Leu	
		210					215					220					
	Ser	Ile	Leu	Pro	Pro	Leu	Arg	Pro	Arg	Leu	Pro	Gly	Gly	Lys	Ala	Ala	
35	225					230					235				240		
	Leu	Ala	Pro	Ala	Leu	Ala	Val	Gly	Gln	Phe	Ala	Ala	Cys	Trp	Leu	Pro	

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	245	250	255
	Tyr Gly Cys Ala Cys Leu Ala Pro Ala Ala Arg Ala Ala Glu Ala Glu		
	260	265	270
5	Ala Ala Val Thr Trp Val Ala Tyr Ser Ala Phe Ala Ala His Pro Phe		
	275	280	285
	Leu Tyr Gly Leu Leu Gln Arg Pro Val Arg Leu Ala Leu Gly Arg Leu		
	290	295	300
	Ser Arg Arg Ala Leu Pro Gly Pro Val Arg Ala Cys Thr Pro Gln Ala		
	305	310	315
10	Trp His Pro Arg Ala Leu Leu Gln Cys Leu Gln Arg Pro Pro Glu Gly		
	325	330	335
	Pro Ala Val Gly Pro Ser Glu Ala Pro Glu Gln Thr Pro Glu Leu Ala		
	340	345	350
15	Gly Gly Arg Ser Pro Ala Tyr Gln Gly Pro Pro Glu Ser Ser Leu Ser		
	355	360	365

## (8) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1008 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

	ATGGAATCAT CTTTCTCATT TGGAGTGATC CTTGCTGTCC TGGCCTCCCT CATCATTGCT	60
25	ACTAACACAC TAGTGGCTGT GGCTGTGCTG CTGTTGATCC ACAAGAATGA TGGTGTCACT	120
	CTCTGCTTCA CCTTGAATCT GGCTGTGGCT GACACCTTGA TTGGTGTGGC CATCTCTGGC	180
	CTACTCACAG ACCAGCTCTC CAGCCCTTCT CGGCCACAC AGAAGACCCT GTGCAGCCTG	240
	CGGATGGCAT TTGTCACTTC TCCGCAGCT GCCTCTGTCC TCACGGTCAT GCTGATCACC	300
	TTTGACAGGT ACCTTGCCAT CAAGCAGCCC TTCCGCTACT TGAAGATCAT GAGTGGGTTC	360
30	GTGGCCGGGG CCTGCATTGC CGGGCTGTGG TTAGTGTCTT ACCTCATTGG CTTCTCCCA	420
	CTCGGAATCC CCATGTTCCA GCAGACTGCC TACAAAGGC AGTCAGCTT CTTTGCTGTA	480
	TTTACCCTC ACTTCGTGCT GACCCTCTCC TCGTGTGGCT TCTTCCAGC CATGCTCCTC	540
	TTTGTCTTCT TCTACTGCGA CATGCTCAAG ATTGCCTCCA TGCACAGCCA GCAGATTCGA	600

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AAGATGGAAC ATGCAGGAGC CATGGCTGGA GGTATCGAT CCCCACGGAC TCCCAGCGAC 660  
 TTCAAAGCTC TCCGTACTGT GTCTGTTCTC ATTGGGAGCT TTGCTCTATC CTGGACCCCC 720  
 TTCCTTATCA CTGGCATTGT GCAGGTGGCC TGCCAGGAGT GTCACCTCTA CCTAGTGCTG 780  
 GAACGGTACC TGTGGCTGCT CGGCGTGGGC AACTCCCTGC TCAACCCACT CATCTATGCC 840  
 5 TATTGGCAGA AGGAGGTGCG ACTGCAGCTC TACCACATGG CCCTAGGAGT GAAGAAGGTG 900  
 CTCACCTCAT TCCTCCTCTT TCTCTCGGCC AGGAATTGTG GCCCAGAGAG GCCCAGGGAA 960  
 AGTTCCTGTC ACATCGTCAC TATCTCCAGC TCAGAGTTTG ATGGCTAA 1008

## (9) INFORMATION FOR SEQ ID NO:8:

- 10 (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 335 amino acids  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS:  
 (D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein

## 15 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

Met Glu Ser Ser Phe Ser Phe Gly Val Ile Leu Ala Val Leu Ala Ser  
 1 5 10 15  
 Leu Ile Ile Ala Thr Asn Thr Leu Val Ala Val Ala Val Leu Leu Leu  
 20 25 30  
 Ile His Lys Asn Asp Gly Val Ser Leu Cys Phe Thr Leu Asn Leu Ala  
 35 40 45  
 Val Ala Asp Thr Leu Ile Gly Val Ala Ile Ser Gly Leu Leu Thr Asp  
 50 55 60  
 25 Gln Leu Ser Ser Pro Ser Arg Pro Thr Gln Lys Thr Leu Cys Ser Leu  
 65 70 75 80  
 Arg Met Ala Phe Val Thr Ser Ser Ala Ala Ala Ser Val Leu Thr Val  
 85 90 95  
 Met Leu Ile Thr Phe Asp Arg Tyr Leu Ala Ile Lys Gln Pro Phe Arg  
 100 105 110  
 30 Tyr Leu Lys Ile Met Ser Gly Phe Val Ala Gly Ala Cys Ile Ala Gly  
 115 120 125  
 Leu Trp Leu Val Ser Tyr Leu Ile Gly Phe Leu Pro Leu Gly Ile Pro  
 130 135 140  
 Met Phe Gln Gln Thr Ala Tyr Lys Gly Gln Cys Ser Phe Phe Ala Val

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	145		150		155		160									
	Phe	His	Pro	His	Phe	Val	Leu	Thr	Leu	Ser	Cys	Val	Gly	Phe	Phe	Pro
					165					170						175
5	Ala	Met	Leu	Leu	Phe	Val	Phe	Phe	Tyr	Cys	Asp	Met	Leu	Lys	Ile	Ala
				180					185					190		
	Ser	Met	His	Ser	Gln	Gln	Ile	Arg	Lys	Met	Glu	His	Ala	Gly	Ala	Met
			195					200						205		
	Ala	Gly	Gly	Tyr	Arg	Ser	Pro	Arg	Thr	Pro	Ser	Asp	Phe	Lys	Ala	Leu
		210					215					220				
10	Arg	Thr	Val	Ser	Val	Leu	Ile	Gly	Ser	Phe	Ala	Leu	Ser	Trp	Thr	Pro
		225				230					235					240
	Phe	Leu	Ile	Thr	Gly	Ile	Val	Gln	Val	Ala	Cys	Gln	Glu	Cys	His	Leu
				245						250					255	
15	Tyr	Leu	Val	Leu	Glu	Arg	Tyr	Leu	Trp	Leu	Leu	Gly	Val	Gly	Asn	Ser
			260					265						270		
	Leu	Leu	Asn	Pro	Leu	Ile	Tyr	Ala	Tyr	Trp	Gln	Lys	Glu	Val	Arg	Leu
			275					280					285			
	Gln	Leu	Tyr	His	Met	Ala	Leu	Gly	Val	Lys	Lys	Val	Leu	Thr	Ser	Phe
		290					295					300				
20	Leu	Leu	Phe	Leu	Ser	Ala	Arg	Asn	Cys	Gly	Pro	Glu	Arg	Pro	Arg	Glu
		305				310					315					320
	Ser	Ser	Cys	His	Ile	Val	Thr	Ile	Ser	Ser	Ser	Glu	Phe	Asp	Gly	
				325						330					335	

## (10) INFORMATION FOR SEQ ID NO:9:

- 25 (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 1413 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

- 30 (ii) MOLECULE TYPE: DNA (genomic)

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

ATGGACACTA	CCATGGAAGC	TGACCTGGGT	GCCACTGGCC	ACAGGCCCCG	CACAGAGCTT	60
GATGATGAGG	ACTCCTACCC	CCAAGGTGGC	TGGGACACGG	TCTTCCTGGT	GGCCCTGCTG	120
CTCCTTGGGC	TGCCAGCCAA	TGGGTTGATG	GCGTGGCTGG	CCGGCTCCCA	GGCCCGGCAT	180
35 GGAGCTGGCA	CGCGTCTGGC	GCTGCTCCTG	CTCAGCCTGG	CCCTCTCTGA	CTTCTGTTC	240



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CTGGCAGCAG CGGCCTTCCA GATCCTAGAG ATCCGGCATG GGGGACACTG GCCGCTGGGG 300  
ACAGCTGCCT GCCGCTTCTA CTACTTCTTA TGGGGCGTGT CCTACTCCTC CGGCCTCTTC 360  
CTGCTGGCCG CCCTCAGCCT CGACCGCTGC CTGCTGGCGC TGTGCCCACA CTGGTACCCT 420  
GGGCACCGCC CAGTCCGCCT GCCCCTCTGG GTCTGCGCCG GTGTCTGGGT GCTGGCCACA 480  
5 CTCTTCAGCG TGCCCTGGCT GGTCTTCCCC GAGGCTGCCG TCTGGTGGTA CGACCTGGTC 540  
ATCTGCCTGG ACTTCTGGGA CAGCGAGGAG CTGTCGCTGA GGATGCTGGA GGTCTCTGGG 600  
GGCTTCCTGC CTTTCCTCCT GCTGCTCGTC TGCCACGTGC TCACCCAGGC CACAGCCTGT 660  
CGCACCTGCC ACCGCCAACA GCAGCCCGCA GCCTGCCGGG GCTTCGCCCC TGTGGCCAGG 720  
ACCATTCTGT CAGCCTATGT GGTCTTGAGG CTGCCCTACC AGCTGGCCCA GCTGCTCTAC 780  
10 CTGGCCTTCC TGTGGGACGT CTACTCTGGC TACCTGCTCT GGGAGGCCCT GGTCTACTCC 840  
GACTACCTGA TCCTACTCAA CAGCTGCCTC AGCCCCTTCC TCTGCCTCAT GGCCAGTGCC 900  
GACCTCCGGA CCCTGTGCG CTCCGTGCTC TCGTCTTCG CGGCAGCTCT CTGCGAGGAG 960  
CGGCCGGGCA GCTTCACGCC CACTGAGCCA CAGACCCAGC TAGATTCTGA GGTCCAAC 1020  
CTGCCAGAGC CGATGGCAGA GGCCAGTCA CAGATGGATC CTGTGGCCCA GCCTCAGGTG 1080  
15 AACCCACAC TCCAGCCAG ATCGGATCCC ACAGCTCAGC CACAGCTGAA CCCTACGGCC 1140  
CAGCCACAGT CGGATCCCAC AGCCAGCCA CAGCTGAACC TCATGGCCCA GCCACAGTCA 1200  
GATTCTGTGG CCCAGCCACA GGCAGACACT AACGTCCAGA CCCCTGCACC TGCTGCCAGT 1260  
TCTGTGCCCA GTCCCTGTGA TGAAGCTTCC CCAACCCCAT CCTCGCATCC TACCCAGGG 1320  
GCCCTTGAGG ACCCAGCCAC ACCTCCTGCC TCTGAAGGAG AAAGCCCCAG CAGCACCCCG 1380  
20 CCAGAGGCGG CCCCAGGCGC AGGCCCCACG TGA 1413

(11) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:

- 25 (A) LENGTH: 468 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

30 Met Asp Thr Thr Met Glu Ala Asp Leu Gly Ala Thr Gly His Arg Pro  
1 5 10 15

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	Arg	Thr	Glu	Leu	Asp	Asp	Glu	Asp	Ser	Tyr	Pro	Gln	Gly	Gly	Trp	Asp	
				20					25					30			
	Thr	Val	Phe	Leu	Val	Ala	Leu	Leu	Leu	Leu	Gly	Leu	Pro	Ala	Asn	Gly	
			35					40					45				
5	Leu	Met	Ala	Trp	Leu	Ala	Gly	Ser	Gln	Ala	Arg	His	Gly	Ala	Gly	Thr	
		50					55					60					
	Arg	Leu	Ala	Leu	Leu	Leu	Leu	Ser	Leu	Ala	Leu	Ser	Asp	Phe	Leu	Phe	
	65					70					75					80	
10	Leu	Ala	Ala	Ala	Ala	Phe	Gln	Ile	Leu	Glu	Ile	Arg	His	Gly	Gly	His	
					85					90					95		
	Trp	Pro	Leu	Gly	Thr	Ala	Ala	Cys	Arg	Phe	Tyr	Tyr	Phe	Leu	Trp	Gly	
				100					105					110			
	Val	Ser	Tyr	Ser	Ser	Gly	Leu	Phe	Leu	Leu	Ala	Ala	Leu	Ser	Leu	Asp	
			115					120					125				
15	Arg	Cys	Leu	Leu	Ala	Leu	Cys	Pro	His	Trp	Tyr	Pro	Gly	His	Arg	Pro	
		130					135					140					
	Val	Arg	Leu	Pro	Leu	Trp	Val	Cys	Ala	Gly	Val	Trp	Val	Leu	Ala	Thr	
	145					150					155					160	
20	Leu	Phe	Ser	Val	Pro	Trp	Leu	Val	Phe	Pro	Glu	Ala	Ala	Val	Trp	Trp	
					165					170					175		
	Tyr	Asp	Leu	Val	Ile	Cys	Leu	Asp	Phe	Trp	Asp	Ser	Glu	Glu	Leu	Ser	
			180						185					190			
	Leu	Arg	Met	Leu	Glu	Val	Leu	Gly	Gly	Phe	Leu	Pro	Phe	Leu	Leu	Leu	
			195					200					205				
25	Leu	Val	Cys	His	Val	Leu	Thr	Gln	Ala	Thr	Arg	Thr	Cys	His	Arg	Gln	
		210					215					220					
	Gln	Gln	Pro	Ala	Ala	Cys	Arg	Gly	Phe	Ala	Arg	Val	Ala	Arg	Thr	Ile	
	225					230					235					240	
30	Leu	Ser	Ala	Tyr	Val	Val	Leu	Arg	Leu	Pro	Tyr	Gln	Leu	Ala	Gln	Leu	
					245					250					255		
	Leu	Tyr	Leu	Ala	Phe	Leu	Trp	Asp	Val	Tyr	Ser	Gly	Tyr	Leu	Leu	Trp	
			260						265					270			
	Glu	Ala	Leu	Val	Tyr	Ser	Asp	Tyr	Leu	Ile	Leu	Leu	Asn	Ser	Cys	Leu	
			275					280					285				
35	Ser	Pro	Phe	Leu	Cys	Leu	Met	Ala	Ser	Ala	Asp	Leu	Arg	Thr	Leu	Leu	
		290					295					300					
	Arg	Ser	Val	Leu	Ser	Ser	Phe	Ala	Ala	Ala	Leu	Cys	Glu	Glu	Arg	Pro	

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	305		310		315		320									
	Gly	Ser	Phe	Thr	Pro	Thr	Glu	Pro	Gln	Thr	Gln	Leu	Asp	Ser	Glu	Gly
					325					330					335	
5	Pro	Thr	Leu	Pro	Glu	Pro	Met	Ala	Glu	Ala	Gln	Ser	Gln	Met	Asp	Pro
			340						345					350		
	Val	Ala	Gln	Pro	Gln	Val	Asn	Pro	Thr	Leu	Gln	Pro	Arg	Ser	Asp	Pro
		355					360						365			
	Thr	Ala	Gln	Pro	Gln	Leu	Asn	Pro	Thr	Ala	Gln	Pro	Gln	Ser	Asp	Pro
		370					375					380				
10	Thr	Ala	Gln	Pro	Gln	Leu	Asn	Leu	Met	Ala	Gln	Pro	Gln	Ser	Asp	Ser
		385				390					395					400
	Val	Ala	Gln	Pro	Gln	Ala	Asp	Thr	Asn	Val	Gln	Thr	Pro	Ala	Pro	Ala
				405						410					415	
15	Ala	Ser	Ser	Val	Pro	Ser	Pro	Cys	Asp	Glu	Ala	Ser	Pro	Thr	Pro	Ser
				420					425					430		
	Ser	His	Pro	Thr	Pro	Gly	Ala	Leu	Glu	Asp	Pro	Ala	Thr	Pro	Pro	Ala
			435					440					445			
	Ser	Glu	Gly	Glu	Ser	Pro	Ser	Ser	Thr	Pro	Pro	Glu	Ala	Ala	Pro	Gly
		450					455					460				
20	Ala	Gly	Pro	Thr												
		465														

## (12) INFORMATION FOR SEQ ID NO:11:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 1248 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

30	ATGTCAGGGA TGGAAAACT TCAGAATGCT TCCTGGATCT ACCAGCAGAA ACTAGAAGAT	60
	CCATTCCAGA AACACCTGAA CAGCACCGAG GAGTATCTGG CCTTCCTCTG CGGACCTCGG	120
	CGCAGCCACT TCTTCCTCCC CGTGTCTGTG GTGTATGTGC CAATTTTGT GGTGGGGGTC	180
	ATTGGCAATG TCCTGGTGTG CCTGGTGATT CTGCAGCACC AGGCTATGAA GACGCCACC	240
	AACTACTACC TCTTCAGCCT GCGGTCTCT GACCTCCTGG TCCTGCTCCT TGAATGCCC	300

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CTGGAGGTCT ATGAGATGTG GCGCAACTAC CCTTTCTTGT TCGGGCCCGT GGGCTGCTAC 360  
 TTCAAGACGG CCCTCTTTGA GACCGTGTGC TTCGCCTCCA TCCTCAGCAT CACCACCGTC 420  
 AGCGTGGAGC GCTACGTGGC CATCCTACAC CCGTTCCGCG CCAAAGTGA GAGCACCCGG 480  
 CGCCGGGCCC TCAGGATCCT CGGCATCGTC TGGGGCTTCT CCGTGCTCTT CTCCCTGCCC 540  
 5 AACACCAGCA TCCATGGCAT CAAGTTCCAC TACTTCCCCA ATGGGTCCCT GGTCCCAGGT 600  
 TCGGCCACCT GTACGGTCAT CAAGCCCATG TGGATCTACA ATTTTCATCAT CCAGGTCACC 660  
 TCCTTCCTAT TCTACCTCCT CCCCATGACT GTCATCAGTG TCCTCTACTA CCTCATGGCA 720  
 CTCAGACTAA AGAAAGACAA ATCTCTTGAG GCAGATGAAG GGAATGCAAA TATTCAAAGA 780  
 CCCTGCAGAA AATCAGTCAA CAAGATGCTG TTTGTCTTGG TCTTAGTGTT TGCTATCTGT 840  
 10 TGGGCCCCGT TCCACATTGA CCGACTCTTC TTCAGCTTTG TGGAGGAGTG GAGTGAATCC 900  
 CTGGCTGCTG TGTTCACCT CGTCCATGTG GTGTCAGGTG TCTTCTTCTA CCTGAGCTCA 960  
 GCTGTCAACC CCATTATCTA TAACCTACTG TCTCGCCGCT TCCAGGCAGC ATTCCAGAAT 1020  
 GTGATCTCTT CTTTCCACAA ACAGTGGCAC TCCCAGCATG ACCCACAGTT GCCACCTGCC 1080  
 CAGCGGAACA TCTTCCTGAC AGAATGCCAC TTTGTGGAGC TGACCGAAGA TATAGGTCCC 1140  
 15 CAATTCCTCAT GTCAGTCATC CATGCACAAC TCTCACCTCC CAACAGCCCT CTCTAGTGAA 1200  
 CAGATGTCAA GAACAACTA TCAAAGCTTC CACTTTAACA AAACCTGA 1248

(13) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:

- 20 (A) LENGTH: 415 amino acids  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS:  
 (D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

25 Met Ser Gly Met Glu Lys Leu Gln Asn Ala Ser Trp Ile Tyr Gln Gln  
 1 5 10 15  
 Lys Leu Glu Asp Pro Phe Gln Lys His Leu Asn Ser Thr Glu Glu Tyr  
 20 25 30  
 30 Leu Ala Phe Leu Cys Gly Pro Arg Arg Ser His Phe Phe Leu Pro Val  
 35 40 45  
 Ser Val Val Tyr Val Pro Ile Phe Val Val Gly Val Ile Gly Asn Val

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	50	55	60
	Leu Val Cys Leu Val Ile Leu Gln His Gln Ala Met Lys Thr Pro Thr		
	65	70	75 80
5	Asn Tyr Tyr Leu Phe Ser Leu Ala Val Ser Asp Leu Leu Val Leu Leu		
		85	90 95
	Leu Gly Met Pro Leu Glu Val Tyr Glu Met Trp Arg Asn Tyr Pro Phe		
		100	105 110
	Leu Phe Gly Pro Val Gly Cys Tyr Phe Lys Thr Ala Leu Phe Glu Thr		
		115	120 125
10	Val Cys Phe Ala Ser Ile Leu Ser Ile Thr Thr Val Ser Val Glu Arg		
		130	135 140
	Tyr Val Ala Ile Leu His Pro Phe Arg Ala Lys Leu Gln Ser Thr Arg		
		145	150 155 160
15	Arg Arg Ala Leu Arg Ile Leu Gly Ile Val Trp Gly Phe Ser Val Leu		
		165	170 175
	Phe Ser Leu Pro Asn Thr Ser Ile His Gly Ile Lys Phe His Tyr Phe		
		180	185 190
	Pro Asn Gly Ser Leu Val Pro Gly Ser Ala Thr Cys Thr Val Ile Lys		
		195	200 205
20	Pro Met Trp Ile Tyr Asn Phe Ile Ile Gln Val Thr Ser Phe Leu Phe		
		210	215 220
	Tyr Leu Leu Pro Met Thr Val Ile Ser Val Leu Tyr Tyr Leu Met Ala		
		225	230 235 240
25	Leu Arg Leu Lys Lys Asp Lys Ser Leu Glu Ala Asp Glu Gly Asn Ala		
		245	250 255
	Asn Ile Gln Arg Pro Cys Arg Lys Ser Val Asn Lys Met Leu Phe Val		
		260	265 270
	Leu Val Leu Val Phe Ala Ile Cys Trp Ala Pro Phe His Ile Asp Arg		
		275	280 285
30	Leu Phe Phe Ser Phe Val Glu Glu Trp Ser Glu Ser Leu Ala Ala Val		
		290	295 300
	Phe Asn Leu Val His Val Val Ser Gly Val Phe Phe Tyr Leu Ser Ser		
		305	310 315 320
35	Ala Val Asn Pro Ile Ile Tyr Asn Leu Leu Ser Arg Arg Phe Gln Ala		
		325	330 335
	Ala Phe Gln Asn Val Ile Ser Ser Phe His Lys Gln Trp His Ser Gln		
		340	345 350

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His Asp Pro Gln Leu Pro Pro Ala Gln Arg Asn Ile Phe Leu Thr Glu  
355 360 365

Cys His Phe Val Glu Leu Thr Glu Asp Ile Gly Pro Gln Phe Pro Cys  
370 375 380

5 Gln Ser Ser Met His Asn Ser His Leu Pro Thr Ala Leu Ser Ser Glu  
385 390 395 400

Gln Met Ser Arg Thr Asn Tyr Gln Ser Phe His Phe Asn Lys Thr  
405 410 415

(14) INFORMATION FOR SEQ ID NO:13:

- 10 (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 1173 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

- 15 (ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

ATGCCAGATA CTAATAGCAC AATCAATTTA TCACTAAGCA CTCGTGTTAC TTTAGCATTT 60  
 TTTATGTCCT TAGTAGCTTT TGCTATAATG CTAGGAAATG CTTTGGTCAT TTTAGCTTTT 120  
 GTGGTGGACA AAAACCTTAG ACATCGAAGT AGTTATTTTT TTCTTAACIT GGCCATCTCT 180  
 20 GACTTCTTTG TGGGTGTGAT CTCCATTCCT TTGTACATCC CTCACACGCT GTTCGAATGG 240  
 GATTTTGGAA AGGAAATCTG TGTATTTTGG CTCCTACTG ACTATCTGTT ATGTACAGCA 300  
 TCTGTATATA ACATTGTCCT CATCAGCTAT GATCGATACC TGTCAGTCTC AAATGCTGTG 360  
 TCTTATAGAA CTCAACATAC TGGGGTCTTG AAGATTGTTA CTCTGATGGT GGCCGTTTGG 420  
 GTGCTGGCCT TCTTAGTGAA TGGGCCAATG ATTCTAGTTT CAGAGTCTTG GAAGGATGAA 480  
 25 GGTAGTGAAT GTGAACCTGG ATTTTTTTTCG GAATGGTACA TCCTTGCCAT CACATCATTC 540  
 TTGGAATTCG TGATCCCAGT CATCTTAGTC GCTTATTTCA ACATGAATAT TTATTGGAGC 600  
 CTGTGGAAGC GTGATCATCT CAGTAGGTGC CAAAGCCATC CTGGACTGAC TGCTGTCTCT 660  
 TCCAACATCT GTGGACACTC ATTCAGAGGT AGACTATCTT CAAGGAGATC TCTTTCTGCA 720  
 TCGACAGAAG TTCCTGCATC CTTTCATTCA GAGAGACAGA GGAGAAAGAG TAGTCTCATG 780  
 30 TTTTCTCTCA GAACCAAGAT GAATAGCAAT ACAATTGCTT CCAAAATGGG TTCCTTCTCC 840  
 CAATCAGATT CTGTAGCTCT TCACCAAAGG GAACATGTTG AACTGCTTAG AGCCAGGAGA 900

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TTAGCCAAGT CACTGGCCAT TCTCTTAGGG GTTTTTGCTG TTTGCTGGGC TCCATATTCT 960  
 CTGTTACAA TTGTCCTTC ATTTTATTCC TCAGCAACAG GTCCTAAATC AGTTTGGTAT 1020  
 AGAATTGCAT TTTGGCTTCA GTGGTTCAAT TCCTTTGTCA ATCCTCTTTT GTATCCATTG 1080  
 TGTCACAAGC GCTTTCAAAA GGCTTTCTTG AAAATATTTT GTATAAAAAA GCAACCTCTA 1140  
 5 CCATCACAAC ACAGTCGGTC AGTATCTTCT TAA 1173

(15) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 390 amino acids  
 (B) TYPE: amino acid  
 10 (C) STRANDEDNESS:  
 (D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

15 Met Pro Asp Thr Asn Ser Thr Ile Asn Leu Ser Leu Ser Thr Arg Val  
 1 5 10 15  
 Thr Leu Ala Phe Phe Met Ser Leu Val Ala Phe Ala Ile Met Leu Gly  
 20 25 30  
 Asn Ala Leu Val Ile Leu Ala Phe Val Val Asp Lys Asn Leu Arg His  
 35 40 45  
 20 Arg Ser Ser Tyr Phe Phe Leu Asn Leu Ala Ile Ser Asp Phe Phe Val  
 50 55 60  
 Gly Val Ile Ser Ile Pro Leu Tyr Ile Pro His Thr Leu Phe Glu Trp  
 65 70 75 80  
 25 Asp Phe Gly Lys Glu Ile Cys Val Phe Trp Leu Thr Thr Asp Tyr Leu  
 85 90 95  
 Leu Cys Thr Ala Ser Val Tyr Asn Ile Val Leu Ile Ser Tyr Asp Arg  
 100 105 110  
 Tyr Leu Ser Val Ser Asn Ala Val Ser Tyr Arg Thr Gln His Thr Gly  
 115 120 125  
 30 Val Leu Lys Ile Val Thr Leu Met Val Ala Val Trp Val Leu Ala Phe  
 130 135 140  
 Leu Val Asn Gly Pro Met Ile Leu Val Ser Glu Ser Trp Lys Asp Glu  
 145 150 155 160  
 35 Gly Ser Glu Cys Glu Pro Gly Phe Phe Ser Glu Trp Tyr Ile Leu Ala  
 165 170 175

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Ile Thr Ser Phe Leu Glu Phe Val Ile Pro Val Ile Leu Val Ala Tyr  
 180 185 190  
 Phe Asn Met Asn Ile Tyr Trp Ser Leu Trp Lys Arg Asp His Leu Ser  
 195 200 205  
 5 Arg Cys Gln Ser His Pro Gly Leu Thr Ala Val Ser Ser Asn Ile Cys  
 210 215 220  
 Gly His Ser Phe Arg Gly Arg Leu Ser Ser Arg Arg Ser Leu Ser Ala  
 225 230 235 240  
 10 Ser Thr Glu Val Pro Ala Ser Phe His Ser Glu Arg Gln Arg Arg Lys  
 245 250 255  
 Ser Ser Leu Met Phe Ser Ser Arg Thr Lys Met Asn Ser Asn Thr Ile  
 260 265 270  
 Ala Ser Lys Met Gly Ser Phe Ser Gln Ser Asp Ser Val Ala Leu His  
 275 280 285  
 15 Gln Arg Glu His Val Glu Leu Leu Arg Ala Arg Arg Leu Ala Lys Ser  
 290 295 300  
 Leu Ala Ile Leu Leu Gly Val Phe Ala Val Cys Trp Ala Pro Tyr Ser  
 305 310 315 320  
 20 Leu Phe Thr Ile Val Leu Ser Phe Tyr Ser Ser Ala Thr Gly Pro Lys  
 325 330 335  
 Ser Val Trp Tyr Arg Ile Ala Phe Trp Leu Gln Trp Phe Asn Ser Phe  
 340 345 350  
 Val Asn Pro Leu Leu Tyr Pro Leu Cys His Lys Arg Phe Gln Lys Ala  
 355 360 365  
 25 Phe Leu Lys Ile Phe Cys Ile Lys Lys Gln Pro Leu Pro Ser Gln His  
 370 375 380  
 Ser Arg Ser Val Ser Ser  
 385 390

## (16) INFORMATION FOR SEQ ID NO:15:

- 30 (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 30 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear  
 35 (ii) MOLECULE TYPE: DNA (genomic)  
 (iv) ANTI-SENSE: NO  
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:



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GGAAAGCTTA ACGATCCCCA GGAGCAACAT

30

(17) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 31 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iv) ANTI-SENSE: YES

10 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

CTGGGATCCT ACGAGAGCAT TTTTCACACA G  
31

(18) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:

- 15 (A) LENGTH: 1128 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

20 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

ATGGCGAACG CGAGCGAGCC GGGTGGCAGC GCGGGCGGCG AGGCGGCCGC CCTGGGCCTC 60  
AAGCTGGCCA CGCTCAGCCT GCTGCTGTGC GTGAGCCTAG CGGGCAACGT GCTGTTTCGCG 120  
CTGCTGATCG TGCGGGAGCG CAGCCTGCAC CGCGCCCCGT ACTACCTGCT GCTCGACCTG 180  
TGCCTGGCCG ACGGGCTGCG CGCGCTCGCC TGCCTCCCGG CCGTCATGCT GCGGGCGCGG 240  
25 CGTGCGGCGG CCGCGGCGGG GCGCCCGCCG GCGCGGCTGG GCTGCAAGCT GCTCGCCTTC 300  
CTGGCCGCGC TCTTCTGCTT CCACGCCGCC TTCCTGCTGC TGGGCGTGGG CGTCACCCGC 360  
TACCTGGCCA TCGCGACCA CCGCTTCTAT GCAGAGCGCC TGGCCGGCTG GCCGTGCGCC 420  
GCCATGCTGG TGTGCGCCGC CTGGGCGCTG GCGCTGGCCG CGGCCTTCCC GCCAGTGCTG 480  
GACGGCGGTG GCGACGACGA GGACGCGCCG TCGCCCTGG AGCAGCGGCC CGACGGCGCC 540  
30 CCCGGCGCGC TGGGCTTCCT GCTGCTGCTG GCCGTGGTGG TGGGCGCCAC GCACCTCGTC 600  
TACCTCCGCC TGCTCTTCTT CATCCACGAC CGCCGCAAGA TCGGGCCCGC GCGCCTGGTG 660

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CCCCCGTCA GCCACGACTG GACCTTCCAC GGCCCGGGCG CCACCGGCCA GGCGGCCGCC      720
AACTGGACGG CGGGCTTCGG CCGCGGGCCC ACGCCGCCCC CGCTTGTGGG CATCCGGCCC      780
GCAGGGCCCG GCCGCGGCGC GCGCCGCCTC CTCGTGCTGG AAGAATTCAA GACGGAGAAG      840
AGGCTGTGCA AGATGTTCTA CGCCGTCACG CTGCTCTTCC TGCTCCTCTG GGGGCCCTAC      900
5  GTCGTGGCCA GCTACCTGCG GGTCTGGTG CGGCCGGCG CCGTCCCCCA GGCCTACCTG      960
ACGGCCTCCG TGTGGCTGAC CTTCGCGCAG GCCGGCATCA ACCCGTCGT GTGCTTCCTC     1020
TTCAACAGGG AGCTGAGGGA CTGCTTCAGG GCCCAGTTCC CCTGCTGCCA GAGCCCCCGG     1080
ACCACCCAGG CGACCCATCC CTGCGACCTG AAAGGCATTG GTTTATGA                    1128

```

(19) INFORMATION FOR SEQ ID NO:18:

- 10 (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 375 amino acids  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS:  
 (D) TOPOLOGY: not relevant

- 15 (ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

```

Met Ala Asn Ala Ser Glu Pro Gly Gly Ser Gly Gly Gly Glu Ala Ala
 1              5              10              15
Ala Leu Gly Leu Lys Leu Ala Thr Leu Ser Leu Leu Leu Cys Val Ser
20              20              25              30
Leu Ala Gly Asn Val Leu Phe Ala Leu Leu Ile Val Arg Glu Arg Ser
              35              40              45
Leu His Arg Ala Pro Tyr Tyr Leu Leu Leu Asp Leu Cys Leu Ala Asp
              50              55              60
25 Gly Leu Arg Ala Leu Ala Cys Leu Pro Ala Val Met Leu Ala Ala Arg
65              70              75              80
Arg Ala Ala Ala Ala Gly Ala Pro Pro Gly Ala Leu Gly Cys Lys
              85              90              95
Leu Leu Ala Phe Leu Ala Ala Leu Phe Cys Phe His Ala Ala Phe Leu
30              100             105             110
Leu Leu Gly Val Gly Val Thr Arg Tyr Leu Ala Ile Ala His His Arg
              115             120             125
Phe Tyr Ala Glu Arg Leu Ala Gly Trp Pro Cys Ala Ala Met Leu Val
              130             135             140

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Cys Ala Ala Trp Ala Leu Ala Leu Ala Ala Ala Phe Pro Pro Val Leu  
 145 150 155 160  
 Asp Gly Gly Gly Asp Asp Glu Asp Ala Pro Cys Ala Leu Glu Gln Arg  
 165 170 175  
 5 Pro Asp Gly Ala Pro Gly Ala Leu Gly Phe Leu Leu Leu Leu Ala Val  
 180 185 190  
 Val Val Gly Ala Thr His Leu Val Tyr Leu Arg Leu Leu Phe Phe Ile  
 195 200 205  
 10 His Asp Arg Arg Lys Met Arg Pro Ala Arg Leu Val Pro Ala Val Ser  
 210 215 220  
 His Asp Trp Thr Phe His Gly Pro Gly Ala Thr Gly Gln Ala Ala Ala  
 225 230 235 240  
 Asn Trp Thr Ala Gly Phe Gly Arg Gly Pro Thr Pro Pro Ala Leu Val  
 245 250 255  
 15 Gly Ile Arg Pro Ala Gly Pro Gly Arg Gly Ala Arg Arg Leu Leu Val  
 260 265 270  
 Leu Glu Glu Phe Lys Thr Glu Lys Arg Leu Cys Lys Met Phe Tyr Ala  
 275 280 285  
 20 Val Thr Leu Leu Phe Leu Leu Leu Trp Gly Pro Tyr Val Val Ala Ser  
 290 295 300  
 Tyr Leu Arg Val Leu Val Arg Pro Gly Ala Val Pro Gln Ala Tyr Leu  
 305 310 315 320  
 Thr Ala Ser Val Trp Leu Thr Phe Ala Gln Ala Gly Ile Asn Pro Val  
 325 330 335  
 25 Val Cys Phe Leu Phe Asn Arg Glu Leu Arg Asp Cys Phe Arg Ala Gln  
 340 345 350  
 Phe Pro Cys Cys Gln Ser Pro Arg Thr Thr Gln Ala Thr His Pro Cys  
 355 360 365  
 30 Asp Leu Lys Gly Ile Gly Leu  
 370 375

(20) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1002 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

```

ATGAACACCA CAGTGATGCA AGGCTTCAAC AGATCTGAGC GGTGCCCCAG AGACACTCGG      60
ATAGTACAGC TGGTATTCCC AGCCCTCTAC ACAGTGGTTT TCTTGACCGG CATCCTGCTG      120
AATACTTTGG CTCTGTGGGT GTTTGTTCAC ATCCCAGCT CCTCCACCTT CATCATCTAC      180
5 CTCAAAAACA CTTTGGTGGC CGACTTGATA ATGACACTCA TGCTTCCTTT CAAAATCCTC      240
TCTGACTCAC ACCTGGCACC CTGGCAGCTC AGAGCTTTTG TGTGTCGTTT TTCTTCGGTG      300
ATATTTTATG AGACCATGTA TGTGGGCATC GTGCTGTTAG GGCTCATAGC CTTTGACAGA      360
TTCCTCAAGA TCATCAGACC TTTGAGAAAT ATTTTCTAA AAAACCTGT TTTTGCAAAA      420
ACGGTCTCAA TCTTCATCTG GTTCTTTTGG TTCTTCATCT CCCTGCCAAA TACGATCTTG      480
10 AGCAACAAGG AAGCAACACC ATCGTCTGTG AAAAAGTGTG CTTCTTAAA GGGGCCTCTG      540
GGGCTGAAAT GGCATCAAAT GGTAAATAAC ATATGCCAGT TTATTTTCTG GACTGTTTTT      600
ATCCTAATGC TTGTGTTTTA TGTGGTTATT GCAAAAAAAG TATATGATTC TTATAGAAAG      660
TCCAAAAGTA AGGACAGAAA AAACAACAAA AAGCTGGAAG GCAAAGTATT TGTTGTCGTG      720
GCTGTCTTCT TTGTGTGTTT TGCTCCATTT CATTTTGCCA GAGTTCATA TACTCACAGT      780
15 CAAACCAACA ATAAGACTGA CTGTAGACTG CAAATCAAC TGTTTATTGC TAAAGAAACA      840
ACTCTCTTTT TGGCAGCAAC TAACATTTGT ATGGATCCCT TAATATACAT ATTCTTATGT      900
AAAAAATTCA CAGAAAAGCT ACCATGTATG CAAGGGAGAA AGACCACAGC ATCAAGCCAA      960
GAAAATCATA GCAGTCAGAC AGACAACATA ACCTTAGGCT GA                          1002

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(21) INFORMATION FOR SEQ ID NO:20:

- 20 (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 333 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: not relevant

- 25 (ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

```

Met Asn Thr Thr Val Met Gln Gly Phe Asn Arg Ser Glu Arg Cys Pro
1           5           10           15
Arg Asp Thr Arg Ile Val Gln Leu Val Phe Pro Ala Leu Tyr Thr Val
30           20           25           30

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Val Phe Leu Thr Gly Ile Leu Leu Asn Thr Leu Ala Leu Trp Val Phe  
 35 40 45

Val His Ile Pro Ser Ser Ser Thr Phe Ile Ile Tyr Leu Lys Asn Thr  
 50 55 60

5 Leu Val Ala Asp Leu Ile Met Thr Leu Met Leu Pro Phe Lys Ile Leu  
 65 70 75 80

Ser Asp Ser His Leu Ala Pro Trp Gln Leu Arg Ala Phe Val Cys Arg  
 85 90 95

10 Phe Ser Ser Val Ile Phe Tyr Glu Thr Met Tyr Val Gly Ile Val Leu  
 100 105 110

Leu Gly Leu Ile Ala Phe Asp Arg Phe Leu Lys Ile Ile Arg Pro Leu  
 115 120 125

Arg Asn Ile Phe Leu Lys Lys Pro Val Phe Ala Lys Thr Val Ser Ile  
 130 135 140

15 Phe Ile Trp Phe Phe Leu Phe Phe Ile Ser Leu Pro Asn Thr Ile Leu  
 145 150 155 160

Ser Asn Lys Glu Ala Thr Pro Ser Ser Val Lys Lys Cys Ala Ser Leu  
 165 170 175

20 Lys Gly Pro Leu Gly Leu Lys Trp His Gln Met Val Asn Asn Ile Cys  
 180 185 190

Gln Phe Ile Phe Trp Thr Val Phe Ile Leu Met Leu Val Phe Tyr Val  
 195 200 205

Val Ile Ala Lys Lys Val Tyr Asp Ser Tyr Arg Lys Ser Lys Ser Lys  
 210 215 220

25 Asp Arg Lys Asn Asn Lys Lys Leu Glu Gly Lys Val Phe Val Val Val  
 225 230 235 240

Ala Val Phe Phe Val Cys Phe Ala Pro Phe His Phe Ala Arg Val Pro  
 245 250 255

30 Tyr Thr His Ser Gln Thr Asn Asn Lys Thr Asp Cys Arg Leu Gln Asn  
 260 265 270

Gln Leu Phe Ile Ala Lys Glu Thr Thr Leu Phe Leu Ala Ala Thr Asn  
 275 280 285

Ile Cys Met Asp Pro Leu Ile Tyr Ile Phe Leu Cys Lys Lys Phe Thr  
 290 295 300

35 Glu Lys Leu Pro Cys Met Gln Gly Arg Lys Thr Thr Ala Ser Ser Gln  
 305 310 315 320

Glu Asn His Ser Ser Gln Thr Asp Asn Ile Thr Leu Gly

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325

330

(22) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 1122 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

10 ATGGCCAACA CTACCGGAGA GCCTGAGGAG GTGAGCGGCG CTCTGTCCCC ACCGTCCGCA 60  
TCAGCTTATG TGAAGCTGGT ACTGCTGGGA CTGATTATGT GCGTGAGCCT GGCGGGTAAC 120  
GCCATCTTGT CCCTGCTGGT GCTCAAGGAG CGTGCCCTGC ACAAGGCTCC TTACTIONTTC 180  
CTGCTGGACC TGTGCCTGGC CGATGGCATA CGCTCTGCCG TCTGCTTCCC CTTTGTGCTG 240  
GCTTCTGTGC GCCACGGCTC TTCATGGACC TTCAGTGAC TCAGCTGCAA GATTGTGGCC 300  
15 TTTATGGCCG TGCTCTTTTG CTTCCATGCG GCCTTCATGC TGTCTGCAT CAGCGTCACC 360  
CGCTACATGG CCATCGCCCA CCACCGCTTC TACGCCAAGC GCATGACACT CTGGACATGC 420  
GCGGCTGTCA TCTGCATGGC CTGGACCCTG TCTGTGGCCA TGGCCTTCCC ACCTGTCTTT 480  
GACGTGGGCA CCTACAAGTT TATTCGGGAG GAGGACCAGT GCATCTTTGA GCATCGCTAC 540  
TTCAAGGCCA ATGACACGCT GGGCTTCATG CTTATGTTGG CTGTGCTCAT GGCAGCTACC 600  
20 CATGCTGTCT ACGGCAAGCT GCTCCTCTTC GAGTATCGTC ACCGCAAGAT GAAGCCAGTG 660  
CAGATGGTGC CAGCCATCAG CCAGAACTGG ACATTCCATG GTCCCGGGGC CACCGGCCAG 720  
GCTGCTGCCA ACTGGATCGC CGGCTTTGGC CGTGGGCCCC TGCCACCAAC CCTGCTGGGT 780  
ATCCGGCAGA ATGGGCATGC AGCCAGCCGG CGGCTACTGG GCATGGACGA GGTCAAGGGT 840  
GAAAAGCAGC TGGGCCGCAT GTTCTACGCG ATCACAATGC TCTTTCTGCT CCTCTGGTCA 900  
25 CCCTACATCG TGGCCTGCTA CTGGCGAGTG TTTGTGAAAG CCTGTGCTGT GCCCCACCGC 960  
TACCTGGCCA CTGCTGTTTG GATGAGCTTC GCCCAGGCTG CCGTCAACCC AATTGTCTGC 1020  
TTCCTGCTCA ACAAGGACCT CAAGAAGTGC CTGACCACTC ACGCCCCCTG CTGGGGCACA 1080  
GGAGGTGCCC CGGCTCCCAG AGAACCCCTAC TGTGTATGT GA 1122

(23) INFORMATION FOR SEQ ID NO:22:

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## (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 373 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

5 (D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: DNA (genomic)

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

	Met	Ala	Asn	Thr	Thr	Gly	Glu	Pro	Glu	Glu	Val	Ser	Gly	Ala	Leu	Ser	
	1				5					10					15		
10	Pro	Pro	Ser	Ala	Ser	Ala	Tyr	Val	Lys	Leu	Val	Leu	Leu	Gly	Leu	Ile	
				20					25					30			
	Met	Cys	Val	Ser	Leu	Ala	Gly	Asn	Ala	Ile	Leu	Ser	Leu	Leu	Val	Leu	
		35						40					45				
15	Lys	Glu	Arg	Ala	Leu	His	Lys	Ala	Pro	Tyr	Tyr	Phe	Leu	Leu	Asp	Leu	
		50					55					60					
	Cys	Leu	Ala	Asp	Gly	Ile	Arg	Ser	Ala	Val	Cys	Phe	Pro	Phe	Val	Leu	
	65				70					75					80		
	Ala	Ser	Val	Arg	His	Gly	Ser	Ser	Trp	Thr	Phe	Ser	Ala	Leu	Ser	Cys	
				85						90					95		
20	Lys	Ile	Val	Ala	Phe	Met	Ala	Val	Leu	Phe	Cys	Phe	His	Ala	Ala	Phe	
				100					105					110			
	Met	Leu	Phe	Cys	Ile	Ser	Val	Thr	Arg	Tyr	Met	Ala	Ile	Ala	His	His	
		115					120					125					
25	Arg	Phe	Tyr	Ala	Lys	Arg	Met	Thr	Leu	Trp	Thr	Cys	Ala	Ala	Val	Ile	
		130				135						140					
	Cys	Met	Ala	Trp	Thr	Leu	Ser	Val	Ala	Met	Ala	Phe	Pro	Pro	Val	Phe	
	145				150					155					160		
	Asp	Val	Gly	Thr	Tyr	Lys	Phe	Ile	Arg	Glu	Glu	Asp	Gln	Cys	Ile	Phe	
				165					170					175			
30	Glu	His	Arg	Tyr	Phe	Lys	Ala	Asn	Asp	Thr	Leu	Gly	Phe	Met	Leu	Met	
				180					185					190			
	Leu	Ala	Val	Leu	Met	Ala	Ala	Thr	His	Ala	Val	Tyr	Gly	Lys	Leu	Leu	
		195					200						205				
35	Leu	Phe	Glu	Tyr	Arg	His	Arg	Lys	Met	Lys	Pro	Val	Gln	Met	Val	Pro	
		210				215					220						
	Ala	Ile	Ser	Gln	Asn	Trp	Thr	Phe	His	Gly	Pro	Gly	Ala	Thr	Gly	Gln	
	225				230					235					240		

Ala Ala Ala Asn Trp Ile Ala Gly Phe Gly Arg Gly Pro Met Pro Pro  
245 250 255

Thr Leu Leu Gly Ile Arg Gln Asn Gly His Ala Ala Ser Arg Arg Leu  
260 265 270

5      Leu Gly Met Asp Glu Val Lys Gly Glu Lys Gln Leu Gly Arg Met Phe  
              275                          280                          285

Tyr Ala Ile Thr Leu Leu Phe Leu Leu Leu Trp Ser Pro Tyr Ile Val  
290 295 300

10 Ala Cys Tyr Trp Arg Val Phe Val Lys Ala Cys Ala Val Pro His Arg  
305 310 315 320

Tyr Leu Ala Thr Ala Val Trp Met Ser Phe Ala Gln Ala Ala Val Asn  
325 330 335

Pro Ile Val Cys Phe Leu Leu Asn Lys Asp Leu Lys Lys Cys Leu Thr  
340 345 350

15 Thr His Ala Pro Cys Trp Gly Thr Gly Gly Ala Pro Ala Pro Arg Glu  
355 360 365

Pro Tyr Cys Val Met  
370

(24) INFORMATION FOR SEQ ID NO:23:

20 (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 1053 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

25 (ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

	ATGGCTTTGG	AACAGAACCA	GTCAACAGAT	TATTATTATG	AGGAAAATGA	AATGAATGGC	60
	ACTTATGACT	ACAGTCAATA	TGAATTGATC	TGTATCAAAG	AAGATGTCAG	AGAATTTGCA	120
	AAAGTTTTCC	TCCCTGTATT	CCTCACAATA	GCTTTCGTCA	TTGGACTTGC	AGGCAATTCC	180
30	ATGGTAGTGG	CAATTTATGC	CTATTACAAG	AAACAGAGAA	CCAAACAGA	TGTGTACATC	240
	CTGAATTTGG	CTGTAGCAGA	TTTACTCCTT	CTATTCACTC	TGCCTTTTTG	GGCTGTTAAT	300
	GCAGTTCATG	GGTGGGTTTT	AGGGAAAATA	ATGTGCAAAA	TAAC TTCAGC	CTTGTACACA	360
	CTAAACTTTG	TCTCTGGAAT	GCAGTTTCTG	GCTTGCATCA	GCATAGACAG	ATATGTGGCA	420
	GTAAC TAATG	TCCCCAGCCA	ATCAGGAGTG	GGAAAACCAT	GCTGGATCAT	CTGTTTCTGT	480



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GTCTGGATGG CTGCCATCTT GCTGAGCATA CCCCAGCTGG TTTTTTATAC AGTAAATGAC 540  
 AATGCTAGGT GCATTCCCAT TTTCCCCCGC TACCTAGGAA CATCAATGAA AGCATTGATT 600  
 CAAATGCTAG AGATCTGCAT TGGATTGTA GTACCCTTTC TTATTATGGG GGTGTGCTAC 660  
 TTTATCACGG CAAGGACACT CATGAAGATG CCAAACATTA AAATATCTCG ACCCCTAAAA 720  
 5 GTTCTGCTCA CAGTCGTTAT AGTTTTCATT GTCACTCAAC TGCCTTATAA CATTGTCAAG 780  
 TTCTGCCGAG CCATAGACAT CATCTACTCC CTGATCACCA GCTGCAACAT GAGCAAACGC 840  
 ATGGACATCG CCATCCAAGT CACAGAAAGC ATTGCACTCT TTCACAGCTG CCTCAACCCA 900  
 ATCCTTTATG TTTTATGGG AGCATCTTTC AAAAAGTACG TTATGAAAGT GGCCAAGAAA 960  
 TATGGGTCCT GGAGAAGACA GAGACAAAGT GTGGAGGAGT TTCCTTTTGA TTCTGAGGGT 1020  
 10 CCTACAGAGC CAACAGTAC TTTTAGCATT TAA 1053

(25) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 350 amino acids  
 (B) TYPE: amino acid  
 15 (C) STRANDEDNESS:  
 (D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

20 Met Ala Leu Glu Gln Asn Gln Ser Thr Asp Tyr Tyr Tyr Glu Glu Asn  
 1 5 10 15  
 Glu Met Asn Gly Thr Tyr Asp Tyr Ser Gln Tyr Glu Leu Ile Cys Ile  
 20 25 30  
 Lys Glu Asp Val Arg Glu Phe Ala Lys Val Phe Leu Pro Val Phe Leu  
 35 40 45  
 25 Thr Ile Ala Phe Val Ile Gly Leu Ala Gly Asn Ser Met Val Val Ala  
 50 55 60  
 Ile Tyr Ala Tyr Tyr Lys Lys Gln Arg Thr Lys Thr Asp Val Tyr Ile  
 65 70 75 80  
 30 Leu Asn Leu Ala Val Ala Asp Leu Leu Leu Leu Phe Thr Leu Pro Phe  
 85 90 95  
 Trp Ala Val Asn Ala Val His Gly Trp Val Leu Gly Lys Ile Met Cys  
 100 105 110  
 Lys Ile Thr Ser Ala Leu Tyr Thr Leu Asn Phe Val Ser Gly Met Gln

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	115	120	125
	Phe Leu Ala Cys Ile Ser Ile Asp Arg Tyr Val Ala Val Thr Asn Val		
	130	135	140
5	Pro Ser Gln Ser Gly Val Gly Lys Pro Cys Trp Ile Ile Cys Phe Cys		
	145	150	155 160
	Val Trp Met Ala Ala Ile Leu Leu Ser Ile Pro Gln Leu Val Phe Tyr		
		165	170 175
	Thr Val Asn Asp Asn Ala Arg Cys Ile Pro Ile Phe Pro Arg Tyr Leu		
		180	185 190
10	Gly Thr Ser Met Lys Ala Leu Ile Gln Met Leu Glu Ile Cys Ile Gly		
		195	200 205
	Phe Val Val Pro Phe Leu Ile Met Gly Val Cys Tyr Phe Ile Thr Ala		
		210	215 220
15	Arg Thr Leu Met Lys Met Pro Asn Ile Lys Ile Ser Arg Pro Leu Lys		
		225	230 235 240
	Val Leu Leu Thr Val Val Ile Val Phe Ile Val Thr Gln Leu Pro Tyr		
		245	250 255
	Asn Ile Val Lys Phe Cys Arg Ala Ile Asp Ile Ile Tyr Ser Leu Ile		
		260	265 270
20	Thr Ser Cys Asn Met Ser Lys Arg Met Asp Ile Ala Ile Gln Val Thr		
		275	280 285
	Glu Ser Ile Ala Leu Phe His Ser Cys Leu Asn Pro Ile Leu Tyr Val		
		290	295 300
25	Phe Met Gly Ala Ser Phe Lys Asn Tyr Val Met Lys Val Ala Lys Lys		
		305	310 315 320
	Tyr Gly Ser Trp Arg Arg Gln Arg Gln Ser Val Glu Glu Phe Pro Phe		
		325	330 335
	Asp Ser Glu Gly Pro Thr Glu Pro Thr Ser Thr Phe Ser Ile		
		340	345 350

30 (26) INFORMATION FOR SEQ ID NO:25:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 1116 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

35

(ii) MOLECULE TYPE: DNA (genomic)

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## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

ATGCCAGGAA ACGCCACCCC AGTGACCACC ACTGCCCCGT GGGCCTCCCT GGGCCTCTCC 60  
GCCAAGACCT GCAACAACGT GTCCTTCGAA GAGAGCAGGA TAGTCCTGGT CGTGGTGTAC 120  
AGCGCGGTGT GCACGCTGGG GGTGCCGGCC AACTGCCTGA CTGCGTGGCT GGCCTGCTG 180  
5 CAGGTACTGC AGGGCAACGT GCTGGCCGTC TACCTGCTCT GCCTGGCACT CTGCGAACTG 240  
CTGTACACAG GCACGCTGCC ACTCTGGGTC ATCTATATCC GCAACCAGCA CCGCTGGACC 300  
CTAGGCCTGC TGGCCTCGAA GGTGACCGCC TACATCTTCT TCTGCAACAT CTACGTCAGC 360  
ATCTCTTCC TGTGCTGCAT CTCCTGCGAC CGCTTCGTGG CCGTGGTGTA CGCGCTGGAG 420  
AGTCGGGGCC GCCGCCGCCG GAGGACCGCC ATCCTCATCT CCGCCTGCAT CTTCATCCTC 480  
10 GTCGGGATCG TTCACTACCC GGTGTTCCAG ACGGAAGACA AGGAGACCTG CTTTGACATG 540  
CTGCAGATGG ACAGCAGGAT TGCCGGGTAC TACTACGCCA GGTTCACCGT TGGCTTTGCC 600  
ATCCCTCTCT CCATCATCGC CTTACCAAC CACCGGATTT TCAGGAGCAT CAAGCAGAGC 660  
ATGGGCTTAA GCGCTGCCCA GAAGGCCAAG GTGAAGCACT CGGCCATCGC GGTGGTTGTC 720  
ATCTTCCTAG TCTGCTTCGC CCCGTACCAC CTGGTTCTCC TCGTCAAAGC CGCTGCCTTT 780  
15 TCCTACTACA GAGGAGACAG GAACGCCATG TCGGGCTTGG AGGAAAGGCT GTACACAGCC 840  
TCTGTGGTGT TTCTGTGCCT GTCCACGGTG AACGGCGTGG CTGACCCCAT TATCTACGTG 900  
CTGGCCACGG ACCATTCCCG CCAAGAAGTG TCCAGAATCC ATAAGGGGTG GAAAGAGTGG 960  
TCCATGAAGA CAGACGTCAC CAGGCTCACC CACAGCAGGG ACACCGAGGA GCTGCAGTCG 1020  
CCCGTGGCCC TTGCAGACCA CTACACCTTC TCCAGGCCCG TGCACCCACC AGGGTCACCA 1080  
20 TGCCCTGCAA AGAGGCTGAT TGAGGAGTCC TGCTGA 1116

## (28) INFORMATION FOR SEQ ID NO:26:

## (i) SEQUENCE CHARACTERISTICS:

- 25 (A) LENGTH: 371 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: not relevant

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

30 Met Pro Gly Asn Ala Thr Pro Val Thr Thr Thr Ala Pro Trp Ala Ser  
1 5 10 15

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	Leu Gly Leu Ser Ala Lys Thr Cys Asn Asn Val Ser Phe Glu Glu Ser	
	20	25 30
	Arg Ile Val Leu Val Val Val Tyr Ser Ala Val Cys Thr Leu Gly Val	
	35	40 45
5	Pro Ala Asn Cys Leu Thr Ala Trp Leu Ala Leu Leu Gln Val Leu Gln	
	50	55 60
	Gly Asn Val Leu Ala Val Tyr Leu Leu Cys Leu Ala Leu Cys Glu Leu	
	65	70 75 80
10	Leu Tyr Thr Gly Thr Leu Pro Leu Trp Val Ile Tyr Ile Arg Asn Gln	
	85	90 95
	His Arg Trp Thr Leu Gly Leu Leu Ala Ser Lys Val Thr Ala Tyr Ile	
	100	105 110
	Phe Phe Cys Asn Ile Tyr Val Ser Ile Leu Phe Leu Cys Cys Ile Ser	
	115	120 125
15	Cys Asp Arg Phe Val Ala Val Val Tyr Ala Leu Glu Ser Arg Gly Arg	
	130	135 140
	Arg Arg Arg Arg Thr Ala Ile Leu Ile Ser Ala Cys Ile Phe Ile Leu	
	145	150 155 160
20	Val Gly Ile Val His Tyr Pro Val Phe Gln Thr Glu Asp Lys Glu Thr	
	165	170 175
	Cys Phe Asp Met Leu Gln Met Asp Ser Arg Ile Ala Gly Tyr Tyr Tyr	
	180	185 190
	Ala Arg Phe Thr Val Gly Phe Ala Ile Pro Leu Ser Ile Ile Ala Phe	
	195	200 205
25	Thr Asn His Arg Ile Phe Arg Ser Ile Lys Gln Ser Met Gly Leu Ser	
	210	215 220
	Ala Ala Gln Lys Ala Lys Val Lys His Ser Ala Ile Ala Val Val Val	
	225	230 235 240
30	Ile Phe Leu Val Cys Phe Ala Pro Tyr His Leu Val Leu Leu Val Lys	
	245	250 255
	Ala Ala Ala Phe Ser Tyr Tyr Arg Gly Asp Arg Asn Ala Met Cys Gly	
	260	265 270
	Leu Glu Glu Arg Leu Tyr Thr Ala Ser Val Val Phe Leu Cys Leu Ser	
	275	280 285
35	Thr Val Asn Gly Val Ala Asp Pro Ile Ile Tyr Val Leu Ala Thr Asp	
	290	295 300

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His Ser Arg Gln Glu Val Ser Arg Ile His Lys Gly Trp Lys Glu Trp  
 305 310 315 320  
 Ser Met Lys Thr Asp Val Thr Arg Leu Thr His Ser Arg Asp Thr Glu  
 325 330 335  
 5 Glu Leu Gln Ser Pro Val Ala Leu Ala Asp His Tyr Thr Phe Ser Arg  
 340 345 350  
 Pro Val His Pro Pro Gly Ser Pro Cys Pro Ala Lys Arg Leu Ile Glu  
 355 360 365  
 10 Glu Ser Cys  
 370

## (28) INFORMATION FOR SEQ ID NO:27:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1113 base pairs  
 (B) TYPE: nucleic acid  
 15 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: DNA (genomic)

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

ATGGCGAACT ATAGCCATGC AGCTGACAAC ATTTTGCAAA ATCTCTCGCC TCTAACAGCC 60  
 20 TTTCTGAAAC TGACTTCCTT GGGTTTCATA ATAGGAGTCA GCGTGGTGGG CAACCTCCTG 120  
 ATCTCCATT TGTAGTGAA AGATAAGACC TTGCATAGAG CACCTTACTA CTTCTGTGTG 180  
 GATCTTTGCT GTTCAGATAT CCTCAGATCT GCAATTGTGT TCCCATTGT GTTCAACTCT 240  
 GTCAAAAATG GCTCTACCTG GACTTATGGG ACTCTGACTT GCAAAGTGAT TGCCTTTCTG 300  
 GGGGTTTTGT CCTGTTTCCA CACTGCTTTC ATGCTCTTCT GCATCAGTGT CACCAGATAC 360  
 25 TTAGCTATCG CCCATCACCG CTTCTATACA AAGAGGCTGA CCTTTTGGAC GTGTCTGGCT 420  
 GTGATCTGTA TGGTGTGGAC TCTGTCTGTG GCCATGGCAT TTCCCCCGGT TTTAGACGTG 480  
 GGCACCTACT CATTCAATTAG GGAGGAAGAT CAATGCACCT TCCAACACCG CTCCTTCAGG 540  
 GCTAATGATT CTTAGGATT TATGCTGCTT CTTGCTCTCA TCCTCCTAGC CACACAGCTT 600  
 GTCTACCTCA AGCTGATATT TTTCGTCCAC GATCGAAGAA AAATGAAGCC AGTCCAGTTT 660  
 30 GTAGCAGCAG TCAGCCAGAA CTGGACTTTT CATGGTCTCTG GAGCCAGTGG CCAGGCAGCT 720  
 GCCAATTGGC TAGCAGGATT TGAAGGGGT CCCACACCAC CCACCTTGCT GGGCATCAGG 780  
 CAAAATGCAA ACACCACAGG CAGAAGAAGG CTATTGGTCT TAGACGAGTT CAAAATGGAG 840

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AAAAGAATCA GCAGAATGTT CTATATAATG ACTTTTCTGT TTCTAACCTT GTGGGGCCCC 900  
 TACCTGGTGG CCTGTTATTG GAGAGTTTTT GCAAGAGGGC CTGTAGTACC AGGGGGATTT 960  
 CTAACAGCTG CTGTCTGGAT GAGTTTGGCC CAAGCAGGAA TCAATCCTTT TGTCTGCATT 1020  
 TTCTCAAACA GGGAGCTGAG GCGCTGTTTC AGCACAACCC TTCTTTACTG CAGAAAATCC 1080  
 5 AGGTTACCAA GGGAACCTTA CTGTGTTATA TGA 1113

(29) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 370 amino acids  
 (B) TYPE: amino acid  
 10 (C) STRANDEDNESS:  
 (D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

15 Met Ala Asn Tyr Ser His Ala Ala Asp Asn Ile Leu Gln Asn Leu Ser  
 1 5 10 15  
 Pro Leu Thr Ala Phe Leu Lys Leu Thr Ser Leu Gly Phe Ile Ile Gly  
 20 25 30  
 Val Ser Val Val Gly Asn Leu Leu Ile Ser Ile Leu Leu Val Lys Asp  
 35 40 45  
 20 Lys Thr Leu His Arg Ala Pro Tyr Tyr Phe Leu Leu Asp Leu Cys Cys  
 50 55 60  
 Ser Asp Ile Leu Arg Ser Ala Ile Cys Phe Pro Phe Val Phe Asn Ser  
 65 70 75 80  
 25 Val Lys Asn Gly Ser Thr Trp Thr Tyr Gly Thr Leu Thr Cys Lys Val  
 85 90 95  
 Ile Ala Phe Leu Gly Val Leu Ser Cys Phe His Thr Ala Phe Met Leu  
 100 105 110  
 Phe Cys Ile Ser Val Thr Arg Tyr Leu Ala Ile Ala His His Arg Phe  
 115 120 125  
 30 Tyr Thr Lys Arg Leu Thr Phe Trp Thr Cys Leu Ala Val Ile Cys Met  
 130 135 140  
 Val Trp Thr Leu Ser Val Ala Met Ala Phe Pro Pro Val Leu Asp Val  
 145 150 155 160  
 Gly Thr Tyr Ser Phe Ile Arg Glu Glu Asp Gln Cys Thr Phe Gln His

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	165	170	175
	Arg Ser Phe Arg Ala Asn Asp Ser Leu Gly Phe Met Leu Leu Leu Ala		
	180	185	190
5	Leu Ile Leu Leu Ala Thr Gln Leu Val Tyr Leu Lys Leu Ile Phe Phe		
	195	200	205
	Val His Asp Arg Arg Lys Met Lys Pro Val Gln Phe Val Ala Ala Val		
	210	215	220
	Ser Gln Asn Trp Thr Phe His Gly Pro Gly Ala Ser Gly Gln Ala Ala		
	225	230	235 240
10	Ala Asn Trp Leu Ala Gly Phe Gly Arg Gly Pro Thr Pro Pro Thr Leu		
	245	250	255
	Leu Gly Ile Arg Gln Asn Ala Asn Thr Thr Gly Arg Arg Arg Leu Leu		
	260	265	270
15	Val Leu Asp Glu Phe Lys Met Glu Lys Arg Ile Ser Arg Met Phe Tyr		
	275	280	285
	Ile Met Thr Phe Leu Phe Leu Thr Leu Trp Gly Pro Tyr Leu Val Ala		
	290	295	300
	Cys Tyr Trp Arg Val Phe Ala Arg Gly Pro Val Val Pro Gly Gly Phe		
	305	310	315 320
20	Leu Thr Ala Ala Val Trp Met Ser Phe Ala Gln Ala Gly Ile Asn Pro		
	325	330	335
	Phe Val Cys Ile Phe Ser Asn Arg Glu Leu Arg Arg Cys Phe Ser Thr		
	340	345	350
25	Thr Leu Leu Tyr Cys Arg Lys Ser Arg Leu Pro Arg Glu Pro Tyr Cys		
	355	360	365
	Val Ile		
	370		

## (30) INFORMATION FOR SEQ ID NO:29:

- (i) SEQUENCE CHARACTERISTICS:
- 30 (A) LENGTH: 1080 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

- 35 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

ATGCAGGTCC CGAACAGCAC CGGCCCGGAC AACGCGACGC TGCAGATGCT GCGGAACCCG

60

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GCGATCGCGG TGGCCCTGCC CGTGGTGTAC TCGCTGGTGG CGGCGGTCAG CATCCCGGGC 120  
AACCTCTTCT CTCTGTGGGT GCTGTGCCGG CGCATGGGGC CCAGATCCCC GTCGGTCATC 180  
TTCATGATCA ACCTGAGCGT CACGGACCTG ATGCTGGCCA GCGTGTGGCC TTTCCAAATC 240  
TACTACCATT GCAACCGCCA CCACTGGGTA TTCGGGGTGC TGCTTTGCAA CGTGGTGACC 300  
5 GTGGCCTTTT ACGCAAACAT GTATTCCAGC ATCCTCACCA TGACCTGTAT CAGCGTGGAG 360  
CGCTTCCTGG GGGTCCTGTA CCCGCTCAGC TCCAAGCGCT GGCGCCGCCG TCGTTACGCG 420  
GTGGCCGCGT GTGCAGGGAC CTGGCTGCTG CTCCTGACCG CCCTGTGCCC GCTGGCGCGC 480  
ACCGATCTCA CCTACCCGGT GCACGCCCTG GGCATCATCA CCTGCTTCGA CGTCTCAAG 540  
TGGACGATGC TCCCCAGCGT GGCCATGTGG GCCGTGTTCC TCTTCACCAT CTTCATCCTG 600  
10 CTGTTCTCTA TCCCGTTCTG GATCACCGTG GCTTGTGTTACA CGGCCACCAT CCTCAAGCTG 660  
TTGCGCACGG AGGAGGCGCA CGGCCGGGAG CAGCGGAGGC GCGCGGTGGG CCTGGCCGCG 720  
GTGGTCTTGC TGGCCTTTGT CACCTGCTTC GCCCCAACA ACTTCGTGCT CCTGGCGCAC 780  
ATCGTGAGCC GCCTGTTCTA CGGCAAGAGC TACTACCACG TGTACAAGCT CACGCTGTGT 840  
CTCAGCTGCC TCAACAACG TCTGGACCCG TTTGTTTATT ACTTTGCGTC CCGGGAATTC 900  
15 CAGCTGCGCC TGCGGGAATA TTTGGGCTGC CGCCGGGTGC CCAGAGACAC CCTGGACACG 960  
CGCCGCGAGA GCCTCTTCTC CGCCAGGACC ACGTCCGTGC GCTCCGAGGC CGGTGCGCAC 1020  
CCTGAAGGGA TGGAGGGAGC CACCAGGCCC GGCCTCCAGA GGCAGGAGAG TGTGTTCTGA 1080

(31) INFORMATION FOR SEQ ID NO:30:

- (i) SEQUENCE CHARACTERISTICS:  
20 (A) LENGTH: 359 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein

- 25 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

Met Gln Val Pro Asn Ser Thr Gly Pro Asp Asn Ala Thr Leu Gln Met  
1 5 10 15

Leu Arg Asn Pro Ala Ile Ala Val Ala Leu Pro Val Val Tyr Ser Leu  
20 25 30

- 30 Val Ala Ala Val Ser Ile Pro Gly Asn Leu Phe Ser Leu Trp Val Leu



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	35	40	45
	Cys Arg Arg Met Gly Pro Arg Ser Pro Ser Val Ile Phe Met Ile Asn 50 55 60		
5	Leu Ser Val Thr Asp Leu Met Leu Ala Ser Val Leu Pro Phe Gln Ile 65 70 75 80		
	Tyr Tyr His Cys Asn Arg His His Trp Val Phe Gly Val Leu Leu Cys 85 90 95		
	Asn Val Val Thr Val Ala Phe Tyr Ala Asn Met Tyr Ser Ser Ile Leu 100 105 110		
10	Thr Met Thr Cys Ile Ser Val Glu Arg Phe Leu Gly Val Leu Tyr Pro 115 120 125		
	Leu Ser Ser Lys Arg Trp Arg Arg Arg Arg Tyr Ala Val Ala Ala Cys 130 135 140		
15	Ala Gly Thr Trp Leu Leu Leu Leu Thr Ala Leu Cys Pro Leu Ala Arg 145 150 155 160		
	Thr Asp Leu Thr Tyr Pro Val His Ala Leu Gly Ile Ile Thr Cys Phe 165 170 175		
	Asp Val Leu Lys Trp Thr Met Leu Pro Ser Val Ala Met Trp Ala Val 180 185 190		
20	Phe Leu Phe Thr Ile Phe Ile Leu Leu Phe Leu Ile Pro Phe Val Ile 195 200 205		
	Thr Val Ala Cys Tyr Thr Ala Thr Ile Leu Lys Leu Leu Arg Thr Glu 210 215 220		
25	Glu Ala His Gly Arg Glu Gln Arg Arg Arg Ala Val Gly Leu Ala Ala 225 230 235 240		
	Val Val Leu Leu Ala Phe Val Thr Cys Phe Ala Pro Asn Asn Phe Val 245 250 255		
	Leu Leu Ala His Ile Val Ser Arg Leu Phe Tyr Gly Lys Ser Tyr Tyr 260 265 270		
30	His Val Tyr Lys Leu Thr Leu Cys Leu Ser Cys Leu Asn Asn Cys Leu 275 280 285		
	Asp Pro Phe Val Tyr Tyr Phe Ala Ser Arg Glu Phe Gln Leu Arg Leu 290 295 300		
35	Arg Glu Tyr Leu Gly Cys Arg Arg Val Pro Arg Asp Thr Leu Asp Thr 305 310 315 320		
	Arg Arg Glu Ser Leu Phe Ser Ala Arg Thr Thr Ser Val Arg Ser Glu 325 330 335		

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Ala Gly Ala His Pro Glu Gly Met Glu Gly Ala Thr Arg Pro Gly Leu  
340 345 350

Gln Arg Gln Glu Ser Val Phe  
355

5 (32) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1503 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
10 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

ATGGAGCGTC CCTGGGAGGA CAGCCCAGGC CCGGAGGGGG CAGCTGAGGG CTCGCCTGTG 60  
CCAGTCGCCG CCGGGGCGCG CTCCGGTGCC GCGGCGAGTG GCACAGGCTG GCAGCCATGG 120  
15 GCTGAGTGCC CGGGACCCAA GGGGAGGGGG CAACTGCTGG CGACCGCCGG CCCTTTGCGT 180  
CGCTGGCCCG CCCCCTCGCC TGCCAGCTCC AGCCCCGCCC CCGGAGCGGC GTCCGCTCAC 240  
TCGGTTCAAG GCAGCGCGAC TCGGGTGGC GCACGACCAG GCGCAGACC TTGGGGCGCG 300  
CGGCCCATGG AGTCGGGGCT GCTGCGGCCG GCGCCGGTGA GCGAGGTCAT CGTCCTGCAT 360  
TACAACTACA CCGGCAAGCT CCGCGGTGCG AGCTACCAGC CGGGTGCCGG CCTGCGCGCC 420  
20 GACGCCGTGG TGTGCCTGGC GGTGTGCGCC TTCATCGTGC TAGAGAATCT AGCCGTGTTG 480  
TTGGTGCTCG GACGCCACCC GCGCTTCCAC GCTCCCATGT TCCTGCTCCT GGGCAGCCTC 540  
ACGTTGTCGG ATCTGCTGGC AGGCGCCGCC TACGCCGCCA ACATCCTACT GTCGGGGCCG 600  
CTCACGCTGA AACTGTCCCC CGCGCTCTGG TTCGCACGGG AGGGAGGCGT CTTGCTGGCA 660  
CTCACTGCGT CCGTGCTGAG CCTCCTGGCC ATCGCGCTGG AGCGCAGCCT CACCATGGCG 720  
25 CGCAGGGGGC CCGCGCCCGT CTCCAGTCGG GGGCGCACGC TGGCGATGGC AGCCGCGGCC 780  
TGGGGCGTGT CGCTGCTCCT CGGGCTCCTG CCAGCGCTGG GCTGGAATTG CCTGGGTCGC 840  
CTGGACGCTT GCTCCACTGT CTTGCCGCTC TACGCCAAGG CCTACGTGCT CTTCTGCGTG 900  
CTCGCCTTCG TGGGCATCCT GGCCGCGATC TGTGCACTCT ACGCGCGCAT CTA CTGCCAG 960  
GTACGCGCCA ACGCGCGGCG CCTGCCGGCA CGGCCCGGGA CTGCGGGGAC CACCTCGACC 1020  
30 CGGGCGCGTC GCAAGCCGCG CTCTCTGGCC TTGCTGCGCA CGCTCAGCGT GGTGCTCCTG 1080

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GCCTTTGTGG CATGTTGGGG CCCCCTCTTC CTGCTGCTGT TGCTCGACGT GGCCTGCCCC 1140  
 GCGCGCACCT GTCCTGTACT CCTGCAGGCC GATCCCTTCC TGGGACTGGC CATGGCCAAC 1200  
 TCACTTCTGA ACCCCATCAT CTACACGCTC ACCAACC GCG 1260  
 CGCCTGGTCT GCTGCGGACG CCACTCCTGC GGCAGAGACC CGAGTGGCTC CCAGCAGTCG 1320  
 5 GCGAGCGCGG CTGAGGCTTC CGGGGGCCTG CGCCGCTGCC TGCCCCCGGG CCTTGATGGG 1380  
 AGCTTCAGCG GCTCGGAGCG CTCATCGCCC CAGCGCGACG GGCTGGACAC CAGCGGCTCC 1440  
 ACAGGCAGCC CCGGTGCACC CACAGCCGCC CGGACTCTGG TATCAGAACC GGCTGCAGAC 1500  
 TGA 1503

(33) INFORMATION FOR SEQ ID NO:32:

- 10 (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 500 amino acids  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS:  
 (D) TOPOLOGY: not relevant

- 15 (ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

Met Glu Arg Pro Trp Glu Asp Ser Pro Gly Pro Glu Gly Ala Ala Glu  
 1 5 10 15  
 Gly Ser Pro Val Pro Val Ala Ala Gly Ala Arg Ser Gly Ala Ala Ala  
 20 20 25 30  
 Ser Gly Thr Gly Trp Gln Pro Trp Ala Glu Cys Pro Gly Pro Lys Gly  
 35 40 45  
 Arg Gly Gln Leu Leu Ala Thr Ala Gly Pro Leu Arg Arg Trp Pro Ala  
 50 55 60  
 25 Pro Ser Pro Ala Ser Ser Ser Pro Ala Pro Gly Ala Ala Ser Ala His  
 65 70 75 80  
 Ser Val Gln Gly Ser Ala Thr Ala Gly Gly Ala Arg Pro Gly Arg Arg  
 85 90 95  
 30 Pro Trp Gly Ala Arg Pro Met Glu Ser Gly Leu Leu Arg Pro Ala Pro  
 100 105 110  
 Val Ser Glu Val Ile Val Leu His Tyr Asn Tyr Thr Gly Lys Leu Arg  
 115 120 125  
 Gly Ala Ser Tyr Gln Pro Gly Ala Gly Leu Arg Ala Asp Ala Val Val  
 130 135 140

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Cys Leu Ala Val Cys Ala Phe Ile Val Leu Glu Asn Leu Ala Val Leu  
 145 150 155 160  
 Leu Val Leu Gly Arg His Pro Arg Phe His Ala Pro Met Phe Leu Leu  
 165 170 175  
 5 Leu Gly Ser Leu Thr Leu Ser Asp Leu Leu Ala Gly Ala Ala Tyr Ala  
 180 185 190  
 Ala Asn Ile Leu Leu Ser Gly Pro Leu Thr Leu Lys Leu Ser Pro Ala  
 195 200 205  
 10 Leu Trp Phe Ala Arg Glu Gly Gly Val Phe Val Ala Leu Thr Ala Ser  
 210 215 220  
 Val Leu Ser Leu Leu Ala Ile Ala Leu Glu Arg Ser Leu Thr Met Ala  
 225 230 235 240  
 Arg Arg Gly Pro Ala Pro Val Ser Ser Arg Gly Arg Thr Leu Ala Met  
 245 250 255  
 15 Ala Ala Ala Ala Trp Gly Val Ser Leu Leu Leu Gly Leu Leu Pro Ala  
 260 265 270  
 Leu Gly Trp Asn Cys Leu Gly Arg Leu Asp Ala Cys Ser Thr Val Leu  
 275 280 285  
 20 Pro Leu Tyr Ala Lys Ala Tyr Val Leu Phe Cys Val Leu Ala Phe Val  
 290 295 300  
 Gly Ile Leu Ala Ala Ile Cys Ala Leu Tyr Ala Arg Ile Tyr Cys Gln  
 305 310 315 320  
 Val Arg Ala Asn Ala Arg Arg Leu Pro Ala Arg Pro Gly Thr Ala Gly  
 325 330 335  
 25 Thr Thr Ser Thr Arg Ala Arg Arg Lys Pro Arg Ser Leu Ala Leu Leu  
 340 345 350  
 Arg Thr Leu Ser Val Val Leu Leu Ala Phe Val Ala Cys Trp Gly Pro  
 355 360 365  
 30 Leu Phe Leu Leu Leu Leu Leu Asp Val Ala Cys Pro Ala Arg Thr Cys  
 370 375 380  
 Pro Val Leu Leu Gln Ala Asp Pro Phe Leu Gly Leu Ala Met Ala Asn  
 385 390 395 400  
 Ser Leu Leu Asn Pro Ile Ile Tyr Thr Leu Thr Asn Arg Asp Leu Arg  
 405 410 415  
 35 His Ala Leu Leu Arg Leu Val Cys Cys Gly Arg His Ser Cys Gly Arg  
 420 425 430  
 Asp Pro Ser Gly Ser Gln Gln Ser Ala Ser Ala Ala Glu Ala Ser Gly

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435                      440                      445  
 Gly Leu Arg Arg Cys Leu Pro Pro Gly Leu Asp Gly Ser Phe Ser Gly  
 450                      455                      460  
 5 Ser Glu Arg Ser Ser Pro Gln Arg Asp Gly Leu Asp Thr Ser Gly Ser  
 465                      470                      475                      480  
 Thr Gly Ser Pro Gly Ala Pro Thr Ala Ala Arg Thr Leu Val Ser Glu  
 485                      490                      495  
 Pro Ala Ala Asp  
 500

10 (34) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1029 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

15 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

ATGCAAGCCG TCGACAATCT CACCTCTGCG CCTGGGAACA CCAGTCTGTG CACCAGAGAC 60  
 TACAAAATCA CCCAGGTCCT CTCCCACTG CTCTACACTG TCCTGTTTTT TGTGGGACTT 120  
 20 ATCACAAATG GCCTGGCGAT GAGGATTTTC TTTCAAATCC GGAGTAAATC AAACCTTTATT 180  
 ATTTTCTTA AGAACACAGT CATTTCTGAT CTTCTCATGA TTCTGACTTT TCCATTCAAA 240  
 ATTCTTAGTG ATGCCAACT GGGAACAGGA CCACTGAGAA CTTTGTGTG TCAAGTTACC 300  
 TCCGTCATAT TTTATTTTAC AATGTATATC AGTATTTTCT TCCTGGGACT GATAACTATC 360  
 GATCGCTACC AGAAGACCAC CAGGCCATTT AAAACATCCA ACCCCAAAAA TCTCTTGGGG 420  
 25 GCTAAGATTC TCTCTGTTGT CATCTGGGCA TTCATGTTCT TACTCTCTTT GCCTAACATG 480  
 ATTCTGACCA ACAGGCAGCC GAGAGACAAG AATGTGAAGA AATGCTCTTT CCTTAAATCA 540  
 GAGTTCGGTC TAGTCTGGCA TGAAATAGTA AATTACATCT GTCAAGTCAT TTTCTGGATT 600  
 AATTTCTTAA TTGTTATTGT ATGTTATACA CTCATTACAA AAGAACTGTA CCGGTCATAC 660  
 GTAAGAACGA GGGGTGTAGG TAAAGTCCCC AGGAAAAAGG TGAACGTCAA AGTTTTCATT 720  
 30 ATCATTGCTG TATTCTTTAT TTGTTTTGTT CTTTCCATT TGCCCCGAAT TCCTTACACC 780  
 CTGAGCCAAA CCCGGGATGT CTTTGAAGTC ACTGCTGAAA ATACTCTGTT CTATGTGAAA 840

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GAGAGCACTC TGTGGTTAAC TTCCTTAAAT GCATGCCTGG ATCCGTTTAT CTATTTTTTC 900  
 CTTTGCAAGT CCTTCAGAAA TTCCTTGATA AGTATGCTGA AGTGCCCCAA TTCTGCAACA 960  
 TCTCTGTCCC AGGACAATAG GAAAAAAGAA CAGGATGGTG GTGACCCAAA TGAAGAGACT 1020  
 CCAATGTAA 1029

## 5 (35) INFORMATION FOR SEQ ID NO:34:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 342 amino acids  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS:  
 (D) TOPOLOGY: not relevant

10

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

Met Gln Ala Val Asp Asn Leu Thr Ser Ala Pro Gly Asn Thr Ser Leu  
 1 5 10 15  
 15 Cys Thr Arg Asp Tyr Lys Ile Thr Gln Val Leu Phe Pro Leu Leu Tyr  
 20 25 30  
 Thr Val Leu Phe Phe Val Gly Leu Ile Thr Asn Gly Leu Ala Met Arg  
 35 40 45  
 20 Ile Phe Phe Gln Ile Arg Ser Lys Ser Asn Phe Ile Ile Phe Leu Lys  
 50 55 60  
 Asn Thr Val Ile Ser Asp Leu Leu Met Ile Leu Thr Phe Pro Phe Lys  
 65 70 75 80  
 Ile Leu Ser Asp Ala Lys Leu Gly Thr Gly Pro Leu Arg Thr Phe Val  
 85 90 95  
 25 Cys Gln Val Thr Ser Val Ile Phe Tyr Phe Thr Met Tyr Ile Ser Ile  
 100 105 110  
 Ser Phe Leu Gly Leu Ile Thr Ile Asp Arg Tyr Gln Lys Thr Thr Arg  
 115 120 125  
 30 Pro Phe Lys Thr Ser Asn Pro Lys Asn Leu Leu Gly Ala Lys Ile Leu  
 130 135 140  
 Ser Val Val Ile Trp Ala Phe Met Phe Leu Leu Ser Leu Pro Asn Met  
 145 150 155 160  
 Ile Leu Thr Asn Arg Gln Pro Arg Asp Lys Asn Val Lys Lys Cys Ser  
 165 170 175  
 35 Phe Leu Lys Ser Glu Phe Gly Leu Val Trp His Glu Ile Val Asn Tyr

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	180	185	190
	Ile Cys Gln Val Ile Phe Trp	Ile Asn Phe Leu Ile Val	Ile Val Cys
	195	200	205
5	Tyr Thr Leu Ile Thr Lys Glu Leu Tyr Arg Ser Tyr Val Arg Thr Arg		
	210	215	220
	Gly Val Gly Lys Val Pro Arg Lys Lys Val Asn Val Lys Val Phe Ile		
	225	230	235 240
	Ile Ile Ala Val Phe Phe Ile Cys Phe Val Pro Phe His Phe Ala Arg		
	245	250	255
10	Ile Pro Tyr Thr Leu Ser Gln Thr Arg Asp Val Phe Asp Cys Thr Ala		
	260	265	270
	Glu Asn Thr Leu Phe Tyr Val Lys Glu Ser Thr Leu Trp Leu Thr Ser		
	275	280	285
15	Leu Asn Ala Cys Leu Asp Pro Phe Ile Tyr Phe Phe Leu Cys Lys Ser		
	290	295	300
	Phe Arg Asn Ser Leu Ile Ser Met Leu Lys Cys Pro Asn Ser Ala Thr		
	305	310	315 320
	Ser Leu Ser Gln Asp Asn Arg Lys Lys Glu Gln Asp Gly Gly Asp Pro		
	325	330	335
20	Asn Glu Glu Thr Pro Met		
	340		
	(36) INFORMATION FOR SEQ ID NO:35:		
	(i) SEQUENCE CHARACTERISTICS:		
25	(A) LENGTH: 1077 base pairs		
	(B) TYPE: nucleic acid		
	(C) STRANDEDNESS: single		
	(D) TOPOLOGY: linear		
	(ii) MOLECULE TYPE: DNA (genomic)		
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:		
30	ATGTCGGTCT GCTACCGTCC CCCAGGGAAC GAGACACTGC TGAGCTGGAA GACTTCGCGG		60
	GCCACAGGCA CAGCCTTCCT GCTGCTGGCG GCGCTGCTGG GGCTGCCTGG CAACGGCTTC		120
	GTGGTGTGGA GCTTGGCGGG CTGGCGGCCT GCACGGGGGC GACCGCTGGC GGCCACGCTT		180
	GTGCTGCACC TGGCGCTGGC CGACGGCGCG GTGCTGCTGC TCACGCCGCT CTTGTGGCC		240
	TTCCTGACCC GGCAGGCCTG GCCGCTGGGC CAGGCGGGCT GCAAGGCGGT GTACTACGTG		300

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TGC GCGCTCA GCATGTACGC CAGCGTGCTG CTCACCGGCC TGCTCAGCCT GCAGCGCTGC 360  
 CTCGCAGTCA CCCGCCCCCTT CCTGGCGCCT CGGCTGCGCA GCCC GGCCCTT GGCCCCCGC 420  
 CTGCTGCTGG CGGTCTGGCT GGCCGCCCTG TTGCTCGCCG TCCCGGCCGC CGTCTACCGC 480  
 CACCTGTGGA GGGACCGCGT ATGCCAGCTG TGCCACCCGT CGCCGGTCCA CGCCGCCGCC 540  
 5 CACCTGAGCC TGGAGACTCT GACCGCTTTC GTGCTTCCTT TCGGGCTGAT GCTCGGCTGC 600  
 TACAGCGTGA CGCTGGCAGC GCTGCGGGGC GCCCCTGGG GCTCCGGGCG GCACGGGGCG 660  
 CGGGTGGGCC GGCTGGTGAG CGCCATCGTG CTTGCCTTCG GCTTGCTCTG GGCCCCCTAC 720  
 CACGCAGTCA ACCTTCTGCA GGCGGTCGCA GCGCTGGCTC CACCGGAAGG GGCCTTGGCG 780  
 AAGCTGGGCG GAGCCGGCCA GCGGCGCGA GCGGGA ACTA CGGCCTTGGC CTTCTCAGT 840  
 10 TCTAGCGTCA ACCCGGTGCT CTACGTCTTC ACCGCTGGAG ATCTGCTGCC CCGGGCAGGT 900  
 CCCCGTTTCC TCACGCGGCT CTTCAAGGC TCTGGGAGG CCCGAGGGG CGGCCGCTCT 960  
 AGGGAAGGGA CCATGGAGCT CCGAACTACC CCTCAGCTGA AAGTGGTGGG GCAGGGCCGC 1020  
 GGCAATGGAG ACCCGGGGGG TGGGATGGAG AAGGACGGTC CGGAATGGGA CCTTTGA 1077

(37) INFORMATION FOR SEQ ID NO:36:

- 15 (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 358 amino acids  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS:  
 (D) TOPOLOGY: not relevant

20 (ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

Met Ser Val Cys Tyr Arg Pro Pro Gly Asn Glu Thr Leu Leu Ser Trp  
 1 5 10 15  
 Lys Thr Ser Arg Ala Thr Gly Thr Ala Phe Leu Leu Leu Ala Ala Leu  
 25 20 25 30  
 Leu Gly Leu Pro Gly Asn Gly Phe Val Val Trp Ser Leu Ala Gly Trp  
 35 40 45  
 Arg Pro Ala Arg Gly Arg Pro Leu Ala Ala Thr Leu Val Leu His Leu  
 50 55 60  
 30 Ala Leu Ala Asp Gly Ala Val Leu Leu Leu Thr Pro Leu Phe Val Ala  
 65 70 75 80  
 Phe Leu Thr Arg Gln Ala Trp Pro Leu Gly Gln Ala Gly Cys Lys Ala



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	85	90	95
	Val Tyr Tyr Val Cys Ala Leu Ser Met Tyr Ala Ser Val Leu Leu Thr		
	100	105	110
5	Gly Leu Leu Ser Leu Gln Arg Cys Leu Ala Val Thr Arg Pro Phe Leu		
	115	120	125
	Ala Pro Arg Leu Arg Ser Pro Ala Leu Ala Arg Arg Leu Leu Leu Ala		
	130	135	140
	Val Trp Leu Ala Ala Leu Leu Leu Ala Val Pro Ala Ala Val Tyr Arg		
	145	150	155
10	His Leu Trp Arg Asp Arg Val Cys Gln Leu Cys His Pro Ser Pro Val		
	165	170	175
	His Ala Ala Ala His Leu Ser Leu Glu Thr Leu Thr Ala Phe Val Leu		
	180	185	190
15	Pro Phe Gly Leu Met Leu Gly Cys Tyr Ser Val Thr Leu Ala Arg Leu		
	195	200	205
	Arg Gly Ala Arg Trp Gly Ser Gly Arg His Gly Ala Arg Val Gly Arg		
	210	215	220
	Leu Val Ser Ala Ile Val Leu Ala Phe Gly Leu Leu Trp Ala Pro Tyr		
	225	230	235
20	His Ala Val Asn Leu Leu Gln Ala Val Ala Ala Leu Ala Pro Pro Glu		
	245	250	255
	Gly Ala Leu Ala Lys Leu Gly Gly Ala Gly Gln Ala Ala Arg Ala Gly		
	260	265	270
25	Thr Thr Ala Leu Ala Phe Phe Ser Ser Ser Val Asn Pro Val Leu Tyr		
	275	280	285
	Val Phe Thr Ala Gly Asp Leu Leu Pro Arg Ala Gly Pro Arg Phe Leu		
	290	295	300
	Thr Arg Leu Phe Glu Gly Ser Gly Glu Ala Arg Gly Gly Gly Arg Ser		
	305	310	315
30	Arg Glu Gly Thr Met Glu Leu Arg Thr Thr Pro Gln Leu Lys Val Val		
	325	330	335
	Gly Gln Gly Arg Gly Asn Gly Asp Pro Gly Gly Gly Met Glu Lys Asp		
	340	345	350
35	Gly Pro Glu Trp Asp Leu		
	355		

(38) INFORMATION FOR SEQ ID NO:37:

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## (i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 1005 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: DNA (genomic)

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

ATGCTGGGGA TCATGGCATG GAATGCAACT TGCAAAACT GGCTGGCAGC AGAGGCTGCC 60  
CTGGAAAAGT ACTACCTTTC CATTTTTTAT GGGATTGAGT TCGTTGTGGG AGTCCTTGGA 120  
10 AATACCATTG TTGTTTACGG CTACATCTTC TCTCTGAAGA ACTGGAACAG CAGTAATATT 180  
TATCTCTTTA ACCTCTCTGT CTCTGACTTA GCTTTTCTGT GCACCCTCCC CATGCTGATA 240  
AGGAGTTATG CCAATGGAAA CTGGATATAT GGAGACGTGC TCTGCATAAG CAACCGATAT 300  
GTGCTTCATG CCAACCTCTA TACCAGCATT CTCTTCTCA CTTTATCAG CATAGATCGA 360  
TACTTGATAA TTAAGTATCC TTTCCGAGAA CACCTTCTGC AAAAGAAAGA GTTTGCTATT 420  
15 TTAATCTCCT TGGCCATTG GGTTTTAGTA ACCTTAGAGT TACTACCCAT ACTTCCCCTT 480  
ATAAATCCTG TTATAACTGA CAATGGCACC ACCTGTAATG ATTTTGCAAG TTCTGGAGAC 540  
CCCAACTACA ACCTCATTTA CAGCATGTGT CTAACACTGT TGGGGTTCCT TATTCCTCTT 600  
TTTGTGATGT GTTCTTTTAA TTACAAGATT GCTCTCTTCC TAAAGCAGAG GAATAGGCAG 660  
GTTGCTACTG CTCTGCCCCT TGAAAAGCCT CTCAACTTGG TCATCATGGC AGTGGTAATC 720  
20 TTCTCTGTGC TTTTACACC CTATCACGTC ATGCGGAATG TGAGGATCGC TTCACGCCTG 780  
GGGAGTTGGA AGCAGTATCA GTGCACTCAG GTCGTCATCA ACTCCTTTTA CATTGTGACA 840  
CGGCCTTTGG CCTTTCTGAA CAGTGTATC AACCTGTCT TCTATTTTCT TTTGGGAGAT 900  
CACTTCAGGG ACATGCTGAT GAATCAACTG AGACACAAC TCAAATCCCT TACATCCTTT 960  
AGCAGATGGG CTCATGAACT CCTACTTTCA TTCAGAGAAA AGTGA 1005

## 25 (39) INFORMATION FOR SEQ ID NO:38:

## (i) SEQUENCE CHARACTERISTICS:

- 30 (A) LENGTH: 334 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: not relevant

## (ii) MOLECULE TYPE: protein

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

	Met	Leu	Gly	Ile	Met	Ala	Trp	Asn	Ala	Thr	Cys	Lys	Asn	Trp	Leu	Ala	
	1				5					10					15		
5	Ala	Glu	Ala	Ala	Leu	Glu	Lys	Tyr	Tyr	Leu	Ser	Ile	Phe	Tyr	Gly	Ile	
					20				25					30			
	Glu	Phe	Val	Val	Gly	Val	Leu	Gly	Asn	Thr	Ile	Val	Val	Tyr	Gly	Tyr	
			35					40						45			
	Ile	Phe	Ser	Leu	Lys	Asn	Trp	Asn	Ser	Ser	Asn	Ile	Tyr	Leu	Phe	Asn	
		50					55					60					
10	Leu	Ser	Val	Ser	Asp	Leu	Ala	Phe	Leu	Cys	Thr	Leu	Pro	Met	Leu	Ile	
	65					70				75					80		
	Arg	Ser	Tyr	Ala	Asn	Gly	Asn	Trp	Ile	Tyr	Gly	Asp	Val	Leu	Cys	Ile	
					85					90					95		
15	Ser	Asn	Arg	Tyr	Val	Leu	His	Ala	Asn	Leu	Tyr	Thr	Ser	Ile	Leu	Phe	
				100					105					110			
	Leu	Thr	Phe	Ile	Ser	Ile	Asp	Arg	Tyr	Leu	Ile	Ile	Lys	Tyr	Pro	Phe	
			115					120					125				
	Arg	Glu	His	Leu	Leu	Gln	Lys	Lys	Glu	Phe	Ala	Ile	Leu	Ile	Ser	Leu	
		130					135					140					
20	Ala	Ile	Trp	Val	Leu	Val	Thr	Leu	Glu	Leu	Leu	Pro	Ile	Leu	Pro	Leu	
	145					150					155					160	
	Ile	Asn	Pro	Val	Ile	Thr	Asp	Asn	Gly	Thr	Thr	Cys	Asn	Asp	Phe	Ala	
				165						170					175		
25	Ser	Ser	Gly	Asp	Pro	Asn	Tyr	Asn	Leu	Ile	Tyr	Ser	Met	Cys	Leu	Thr	
				180					185					190			
	Leu	Leu	Gly	Phe	Leu	Ile	Pro	Leu	Phe	Val	Met	Cys	Phe	Phe	Tyr	Tyr	
			195					200					205				
	Lys	Ile	Ala	Leu	Phe	Leu	Lys	Gln	Arg	Asn	Arg	Gln	Val	Ala	Thr	Ala	
		210					215						220				
30	Leu	Pro	Leu	Glu	Lys	Pro	Leu	Asn	Leu	Val	Ile	Met	Ala	Val	Val	Ile	
	225					230					235					240	
	Phe	Ser	Val	Leu	Phe	Thr	Pro	Tyr	His	Val	Met	Arg	Asn	Val	Arg	Ile	
				245						250					255		
35	Ala	Ser	Arg	Leu	Gly	Ser	Trp	Lys	Gln	Tyr	Gln	Cys	Thr	Gln	Val	Val	
				260					265					270			
	Ile	Asn	Ser	Phe	Tyr	Ile	Val	Thr	Arg	Pro	Leu	Ala	Phe	Leu	Asn	Ser	

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280

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Val Ile Asn Pro Val Phe Tyr Phe Leu Leu Gly Asp His Phe Arg Asp  
 290 295 300

5 Met Leu Met Asn Gln Leu Arg His Asn Phe Lys Ser Leu Thr Ser Phe  
 305 310 315 320

Ser Arg Trp Ala His Glu Leu Leu Leu Ser Phe Arg Glu Lys  
 325 330

(40) INFORMATION FOR SEQ ID NO:39:

(i) SEQUENCE CHARACTERISTICS:

- 10 (A) LENGTH: 1296 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

15 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

ATGCAGGCGC TTAACATTAC CCCGGAGCAG TTCTCTCGGC TGCTGCGGGA CCACAACCTG 60  
 ACGCGGGAGC AGTTCATCGC TCTGTACCGG CTGCGACCGC TCGTCTACAC CCCAGAGCTG 120  
 CCGGGACGCG CCAAGCTGGC CCTCGTGCTC ACCGGCGTGC TCATCTTCGC CCTGGCGCTC 180  
 TTTGGCAATG CTCTGGTGTT CTACGTGGTG ACCCGCAGCA AGGCCATGCG CACCGTCACC 240  
 20 AACATCTTTA TCTGCTCCTT GCGGCTCAGT GACCTGCTCA TCACCTTCTT CTGCATTCCC 300  
 GTCACCATGC TCCAGAACAT TTCCGACAAC TGGCTGGGGG GTGCTTTTCAT TTGCAAGATG 360  
 GTGCCATTTG TCCAGTCTAC CGCTGTTGTG ACAGAAATGC TCACTATGAC CTGCATTGCT 420  
 GTGGAAAGGC ACCAGGGACT TGTGCATCCT TTTAAAATGA AGTGGCAATA CACCAACCGA 480  
 AGGGCTTTCA CAATGCTAGG TGTGGTCTGG CTGGTGGCAG TCATCGTAGG ATCACCCATG 540  
 25 TGGCACGTGC AACAACTTGA GATCAAATAT GACTTCCTAT ATGAAAAGGA ACACATCTGC 600  
 TGCTTAGAAG AGTGGACCAG CCCTGTGCAC CAGAAGATCT ACACCACCTT CATCCTTGTC 660  
 ATCCTCTTCC TCCTGCCTCT TATGGTGATG CTTATTCTGT ACAGTAAAAT TGGTTATGAA 720  
 CTTTGGATAA AGAAAAGAGT TGGGGATGGT TCAGTGCTTC GAACTATTCA TGGAAAAGAA 780  
 ATGTCCAAAA TAGCCAGGAA GAAGAAACGA GCTGTCATTA TGATGGTGAC AGTGGTGGCT 840  
 30 CTCTTTGCTG TGTGCTGGGC ACCATTCCAT GTTGTCCATA TGATGATTGA ATACAGTAAT 900  
 TTTGAAAAGG AATATGATGA TGTACAATC AAGATGATTT TTGCTATCGT GCAAATTATT 960

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GGATTTTCCA ACTCCATCTG TAATCCCATT GTCTATGCAT TTATGAATGA AAACCTTCAAA 1020  
 AAAAAATGTTT TGTCTGCAGT TTGTTATTGC ATAGTAAATA AAACCTTCTC TCCAGCACAA 1080  
 AGGCATGGAA ATTCAGGAAT TACAATGATG CGGAAGAAAG CAAAGTTTTC CCTCAGAGAG 1140  
 AATCCAGTGG AGGAAACCAA AGGAGAAGCA TTCAGTGATG GCAACATTGA AGTCAAATTG 1200  
 5 TGTGAACAGA CAGAGGAGAA GAAAAAGCTC AAACGACATC TTGCTCTCTT TAGGTCTGAA 1260  
 CTGGCTGAGA ATTCTCCTTT AGACAGTGGG CATTA 1296

(41) INFORMATION FOR SEQ ID NO:40:

(i) SEQUENCE CHARACTERISTICS:

- 10 (A) LENGTH: 431 amino acids  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS:  
 (D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

15 Met Gln Ala Leu Asn Ile Thr Pro Glu Gln Phe Ser Arg Leu Leu Arg  
 1 5 10 15  
 Asp His Asn Leu Thr Arg Glu Gln Phe Ile Ala Leu Tyr Arg Leu Arg  
 20 25 30  
 Pro Leu Val Tyr Thr Pro Glu Leu Pro Gly Arg Ala Lys Leu Ala Leu  
 35 40 45  
 Val Leu Thr Gly Val Leu Ile Phe Ala Leu Ala Leu Phe Gly Asn Ala  
 50 55 60  
 Leu Val Phe Tyr Val Val Thr Arg Ser Lys Ala Met Arg Thr Val Thr  
 65 70 75 80  
 25 Asn Ile Phe Ile Cys Ser Leu Ala Leu Ser Asp Leu Leu Ile Thr Phe  
 85 90 95  
 Phe Cys Ile Pro Val Thr Met Leu Gln Asn Ile Ser Asp Asn Trp Leu  
 100 105 110  
 Gly Gly Ala Phe Ile Cys Lys Met Val Pro Phe Val Gln Ser Thr Ala  
 30 115 120 125  
 Val Val Thr Glu Met Leu Thr Met Thr Cys Ile Ala Val Glu Arg His  
 130 135 140  
 Gln Gly Leu Val His Pro Phe Lys Met Lys Trp Gln Tyr Thr Asn Arg  
 145 150 155 160

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Arg Ala Phe Thr Met Leu Gly Val Val Trp Leu Val Ala Val Ile Val  
165 170 175

Gly Ser Pro Met Trp His Val Gln Gln Leu Glu Ile Lys Tyr Asp Phe  
180 185 190

5 Leu Tyr Glu Lys Glu His Ile Cys Cys Leu Glu Glu Trp Thr Ser Pro  
195 200 205

Val His Gln Lys Ile Tyr Thr Thr Phe Ile Leu Val Ile Leu Phe Leu  
210 215 220

10 Leu Pro Leu Met Val Met Leu Ile Leu Tyr Ser Lys Ile Gly Tyr Glu  
225 230 235 240

Leu Trp Ile Lys Lys Arg Val Gly Asp Gly Ser Val Leu Arg Thr Ile  
245 250 255

His Gly Lys Glu Met Ser Lys Ile Ala Arg Lys Lys Lys Arg Ala Val  
260 265 270

15 Ile Met Met Val Thr Val Val Ala Leu Phe Ala Val Cys Trp Ala Pro  
275 280 285

Phe His Val Val His Met Met Ile Glu Tyr Ser Asn Phe Glu Lys Glu  
290 295 300

20 Tyr Asp Asp Val Thr Ile Lys Met Ile Phe Ala Ile Val Gln Ile Ile  
305 310 315 320

Gly Phe Ser Asn Ser Ile Cys Asn Pro Ile Val Tyr Ala Phe Met Asn  
325 330 335

Glu Asn Phe Lys Lys Asn Val Leu Ser Ala Val Cys Tyr Cys Ile Val  
340 345 350

25 Asn Lys Thr Phe Ser Pro Ala Gln Arg His Gly Asn Ser Gly Ile Thr  
355 360 365

Met Met Arg Lys Lys Ala Lys Phe Ser Leu Arg Glu Asn Pro Val Glu  
370 375 380

30 Glu Thr Lys Gly Glu Ala Phe Ser Asp Gly Asn Ile Glu Val Lys Leu  
385 390 395 400

Cys Glu Gln Thr Glu Glu Lys Lys Lys Leu Lys Arg His Leu Ala Leu  
405 410 415

Phe Arg Ser Glu Leu Ala Glu Asn Ser Pro Leu Asp Ser Gly His  
420 425 430

35 (42) INFORMATION FOR SEQ ID NO:41:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 24 base pairs

- 50 -

- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

5 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

CTGTGTACAG CAGTTCGCAG AGTG

24

(43) INFORMATION FOR SEQ ID NO:42:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 24 base pairs
- 10 (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

15 GAGTGCCAGG CAGAGCAGGT AGAC

24

(44) INFORMATION FOR SEQ ID NO:43:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 31 base pairs
- 20 (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

25 CCCGAATTCC TGCTTGCTCC CAGCTTGGCC C

31

(45) INFORMATION FOR SEQ ID NO:44:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 32 base pairs
- 30 (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iv) ANTI-SENSE: YES

- 51 -

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:

TGTGGATCCT GCTGTCAAAG GTCCCATTCC GG

32

(46) INFORMATION FOR SEQ ID NO:45:

(i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 20 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

10 (iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:

TCACAATGCT AGGTGTGGTC

20

(47) INFORMATION FOR SEQ ID NO:46:

(i) SEQUENCE CHARACTERISTICS:

- 15 (A) LENGTH: 22 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

20 (iv) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:

TGCATAGACA ATGGGATTAC AG

22

(48) INFORMATION FOR SEQ ID NO:47:

(i) SEQUENCE CHARACTERISTICS:

- 25 (A) LENGTH: 511 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

30 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

TCACAATGCT AGGTGTGGTC TGGCTGGTGG CAGTCATCGT AGGATCACCC ATGTGGCAGC

60

TGCAACAAC TGAATCAAAA TATGACTTCC TATATGAAAA GGAACACATC TGCTGCTTAG

120



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AAGAGTGGAC CAGCCCTGTG CACCAGAAGA TCTACACCAC CTTCATCCTT GTCATCCTCT 180  
TCCTCCTGCC TCTTATGGTG ATGCTTATTC TGTACGTAAA ATTGGTTATG AACTTTGGAT 240  
AAAGAAAAGA GTTGGGGATG GTTCAGTGCT TCGAACTATT CATGGAAAAG AAATGTCCAA 300  
AATAGCCAGG AAGAAGAAAC GAGCTGTCAT TATGATGGTG ACAGTGGTGG CTCTCTTTGC 360  
5 TGTGTGCTGG GCACCATTCC ATGTTGTCCA TATGATGATT GAATACAGTA ATTTTGAAAA 420  
GGAATATGAT GATGTCACAA TCAAGATGAT TTTTGCTATC GTGCAAATTA TTGGATTTTC 480  
CAACTCCATC TGTAATCCCA TTGTCTATGC A 511

(49) INFORMATION FOR SEQ ID NO:48:

- (i) SEQUENCE CHARACTERISTICS:  
10 (A) LENGTH: 21 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear  
  
(ii) MOLECULE TYPE: DNA (genomic)  
  
15 (iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:

CTGCTTAGAA GAGTGGACCA G 21

(50) INFORMATION FOR SEQ ID NO:49:

- (i) SEQUENCE CHARACTERISTICS:  
20 (A) LENGTH: 22 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear  
  
(ii) MOLECULE TYPE: DNA (genomic)  
  
25 (iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:49:

CTGTGCACCA GAAGATCTAC AC 22

(51) INFORMATION FOR SEQ ID NO:50:

- (i) SEQUENCE CHARACTERISTICS:  
30 (A) LENGTH: 21 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

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(ii) MOLECULE TYPE: DNA (genomic)

(iv) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:50:

CAAGGATGAA GGTGGTGTAG A

21

5 (52) INFORMATION FOR SEQ ID NO:51:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 23 base pairs

(B) TYPE: nucleic acid

10 (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iv) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:

GTGTAGATCT TCTGGTGCAC AGG

23

15 (53) INFORMATION FOR SEQ ID NO:52:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21 base pairs

(B) TYPE: nucleic acid

20 (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:

GCAATGCAGG TCATAGTGAG C

21

(54) INFORMATION FOR SEQ ID NO:53:

25 (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 27 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

30 (ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: YES

(iv) ANTI-SENSE: YES

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:

TGGAGCATGG TGACGGGAAT GCAGAAG

27

(55) INFORMATION FOR SEQ ID NO:54:

(i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 27 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

- 10 (iv) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:54:

GTGATGAGCA GGTCAGTGAAG CGCCAAG

27

(56) INFORMATION FOR SEQ ID NO:55:

(i) SEQUENCE CHARACTERISTICS:

- 15 (A) LENGTH: 23 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

- 20 (iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:

GCAATGCAGG CGCTTAACAT TAC

23

(57) INFORMATION FOR SEQ ID NO:56:

(i) SEQUENCE CHARACTERISTICS:

- 25 (A) LENGTH: 22 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

- 30 (iv) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:56:

TTGGGTTACA ATCTGAAGGG CA

22

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(58) INFORMATION FOR SEQ ID NO:57:

- (i) SEQUENCE CHARACTERISTICS:  
    (A) LENGTH: 23 base pairs  
    (B) TYPE: nucleic acid  
    (C) STRANDEDNESS: single  
    (D) TOPOLOGY: linear

5

(ii) MOLECULE TYPE: DNA (genomic)

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:57:

10 ACTCCGTGTC CAGCAGGACT CTG

23

(58) INFORMATION FOR SEQ ID NO:58:

- (i) SEQUENCE CHARACTERISTICS:  
    (A) LENGTH: 24 base pairs  
    (B) TYPE: nucleic acid  
    (C) STRANDEDNESS: single  
    (D) TOPOLOGY: linear

15

(ii) MOLECULE TYPE: DNA (genomic)

(iv) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:58:

20 TGGGTGTTCC TGGACCCTCA CGTG

24

(58) INFORMATION FOR SEQ ID NO:59:

- (i) SEQUENCE CHARACTERISTICS:  
    (A) LENGTH: 29 base pairs  
    (B) TYPE: nucleic acid  
    (C) STRANDEDNESS: single  
    (D) TOPOLOGY: linear

25

(ii) MOLECULE TYPE: DNA (genomic)

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:59:

30 CAGGCCTTGG ATTTTAATGT CAGGGATGG

29

(61) INFORMATION FOR SEQ ID NO:60:

- (i) SEQUENCE CHARACTERISTICS:  
    (A) LENGTH: 27 base pairs

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- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

5 (iv) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:60:

GGAGAGTCAG CTCTGAAAGA ATTCAGG

27

(62) INFORMATION FOR SEQ ID NO:61:

(i) SEQUENCE CHARACTERISTICS:

- 10 (A) LENGTH: 27 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

15 (iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:61:

TGATGTGATG CCAGATACTA ATAGCAC

27

(63) INFORMATION FOR SEQ ID NO:62:

(i) SEQUENCE CHARACTERISTICS:

- 20 (A) LENGTH: 27 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

25 (iv) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:62:

CCTGATTCAT TTAGGTGAGA TTGAGAC

27

(64) INFORMATION FOR SEQ ID NO:63:

(i) SEQUENCE CHARACTERISTICS:

- 30 (A) LENGTH: 26 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

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(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:63:

CCCAAGCTTC CCCAGGTGTA TTTGAT

26

(3) INFORMATION FOR SEQ ID NO:63:

- 5 (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 26 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

10 (ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:64:

GTTGGATCCA CATAATGCAT TTTCTC

26

(66) INFORMATION FOR SEQ ID NO:65:

- 15 (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 1080 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

20 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:65:

ATGATTCTCA ACTCTTCTAC TGAAGATGGT ATTAAAAGAA TCCAAGATGA TTGTCCCAAA 60  
GCTGGAAGGC ATAATTACAT ATTTGTCATG ATTCCTACTT TATACAGTAT CATCTTTGTG 120  
GTGGGAATAT TTGGAAACAG CTGGGTGGTG ATAGTCATTT ACTTTTATAT GAAGCTGAAG 180  
ACTGTGGCCA GTGTTTTTCT TTTGAATTTA GCACTGGCTG ACTTATGCTT TTTACTGACT 240  
25 TTGCCACTAT GGGCTGTCTA CACAGCTATG GAATACCGCT GGCCCTTTGG CAATTACCTA 300  
TGTAAGATTG CTTCAGCCAG CGTCAGTTTC AACCTGTACG CTAGTGTGTT TCTACTCAG 360  
TGTCTCAGCA TTGATCGATA CCTGGCTATT GTTCACCCAA TGAAGTCCCG CCTTCGACGC 420  
ACAATGCTTG TAGCCAAAGT CACCTGCATC ATCATTGGC TGCTGGCAGG CTTGGCCAGT 480  
TTGCCAGCTA TAATCCATCG AAATGTATTT TTCATTGAGA ACACCAATAT TACAGTTTGT 540  
30 GCTTCCATT ATGAGTCCCA AAATTCAACC CTTCCGATAG GGCTGGGCCT GACCAAAAAT 600

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ATACTGGGTT TCCTGTTTCC TTTTCTGATC ATTCTTACAA GTTATACTCT TATTTGGAAG 660  
 GCCCTAAAGA AGGCTTATGA AATTCAGAAG AACAAACCAA GAAATGATGA TATTTTAAAG 720  
 ATAATTATGG CAATTGTGCT TTTCTTTTTC TTTTCCTGGA TTCCCCACCA AATATTCAC 780  
 TTTCTGGATG TATTGATTCA ACTAGGCATC ATACGTGACT GTAGAATTGC AGATATTGTG 840  
 5 GACACGGCCA TGCCTATCAC CATTGTGATA GCTTATTTTA ACAATTGCCT GAATCCTCTT 900  
 TTTTATGGCT TTCTGGGGAA AAAATTTTAA AGATATTTTC TCCAGCTTCT AAAATATATT 960  
 CCCCCAAAAG CCAAATCCCA CTCAAACCTT TCAACAAAAA TGAGCACGCT TTCCTACCGC 1020  
 CCCTCAGATA ATGTAAGCTC ATCCACCAAG AAGCCTGCAC CATGTTTTGA GGTGAGTGA 1080

(67) INFORMATION FOR SEQ ID NO:66:

- 10 (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 359 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: not relevant

- 15 (ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:66:

Met Ile Leu Asn Ser Ser Thr Glu Asp Gly Ile Lys Arg Ile Gln Asp .  
 1 5 10 15  
 Asp Cys Pro Lys Ala Gly Arg His Asn Tyr Ile Phe Val Met Ile Pro  
 20 20 25 30  
 Thr Leu Tyr Ser Ile Ile Phe Val Val Gly Ile Phe Gly Asn Ser Leu  
 35 40 45  
 Val Val Ile Val Ile Tyr Phe Tyr Met Lys Leu Lys Thr Val Ala Ser  
 50 55 60  
 25 Val Phe Leu Leu Asn Leu Ala Leu Ala Asp Leu Cys Phe Leu Leu Thr  
 65 70 75 80  
 Leu Pro Leu Trp Ala Val Tyr Thr Ala Met Glu Tyr Arg Trp Pro Phe  
 85 90 95  
 Gly Asn Tyr Leu Cys Lys Ile Ala Ser Ala Ser Val Ser Phe Asn Leu  
 30 100 105 110  
 Tyr Ala Ser Val Phe Leu Leu Thr Cys Leu Ser Ile Asp Arg Tyr Leu  
 115 120 125  
 Ala Ile Val His Pro Met Lys Ser Arg Leu Arg Arg Thr Met Leu Val

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	130		135		140
	Ala Lys Val Thr Cys Ile Ile Ile Trp Leu Leu Ala Gly Leu Ala Ser				
	145		150		155 160
5	Leu Pro Ala Ile Ile His Arg Asn Val Phe Phe Ile Glu Asn Thr Asn				
			165	170	175
	Ile Thr Val Cys Ala Phe His Tyr Glu Ser Gln Asn Ser Thr Leu Pro				
			180	185	190
	Ile Gly Leu Gly Leu Thr Lys Asn Ile Leu Gly Phe Leu Phe Pro Phe				
			195	200	205
10	Leu Ile Ile Leu Thr Ser Tyr Thr Leu Ile Trp Lys Ala Leu Lys Lys				
			210	215	220
	Ala Tyr Glu Ile Gln Lys Asn Lys Pro Arg Asn Asp Asp Ile Phe Lys				
			225	230	235 240
15	Ile Ile Met Ala Ile Val Leu Phe Phe Phe Phe Ser Trp Ile Pro His				
			245	250	255
	Gln Ile Phe Thr Phe Leu Asp Val Leu Ile Gln Leu Gly Ile Ile Arg				
			260	265	270
	Asp Cys Arg Ile Ala Asp Ile Val Asp Thr Ala Met Pro Ile Thr Ile				
			275	280	285
20	Cys Ile Ala Tyr Phe Asn Asn Cys Leu Asn Pro Leu Phe Tyr Gly Phe				
			290	295	300
	Leu Gly Lys Lys Phe Lys Arg Tyr Phe Leu Gln Leu Leu Lys Tyr Ile				
			305	310	315 320
25	Pro Pro Lys Ala Lys Ser His Ser Asn Leu Ser Thr Lys Met Ser Thr				
			325	330	335
	Leu Ser Tyr Arg Pro Ser Asp Asn Val Ser Ser Ser Thr Lys Lys Pro				
			340	345	350
	Ala Pro Cys Phe Glu Val Glu				
			355		

30 (68) INFORMATION FOR SEQ ID NO:67:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 27 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

35 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)



- 60 -

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:67:

ACCATGGGCA GCCCCTGGAA CGGCAGC

27

(69) INFORMATION FOR SEQ ID NO:68:

(i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 39 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

10 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:68:

AGAACCACCA CCAGCAGGAC GCGGACGGTC TGCCGGTGG

39

(70) INFORMATION FOR SEQ ID NO:69:

(i) SEQUENCE CHARACTERISTICS:

- 15 (A) LENGTH: 39 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:69:

20 GTCCGCGTCC TGCTGGTGGT GGTTCTGGCA TTTATAATT

39

(71) INFORMATION FOR SEQ ID NO:70:

(i) SEQUENCE CHARACTERISTICS:

- 25 (A) LENGTH: 33 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:70:

CCTGGATCCT TATCCCATCG TCTTCACGTT AGC

33

30 (72) INFORMATION FOR SEQ ID NO:71:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 26 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single

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(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:71:

5 CTGGAATTCT CCTGCCAGCA TGGTGA  
26

(73) INFORMATION FOR SEQ ID NO:72:

(i) SEQUENCE CHARACTERISTICS:

10 (A) LENGTH: 30 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iv) ANTI-SENSE: YES

15 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:72:

GCAGGATCCT ATATTGCGTG CTCTGTCCCC  
30

(74) INFORMATION FOR SEQ ID NO:73:

(i) SEQUENCE CHARACTERISTICS:

20 (A) LENGTH: 999 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

25 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:73:

ATGGTGAACT CCACCCACCG TGGGATGCAC ACTTCTCTGC ACCTCTGGAA CCGCAGCAGT 60  
TACAGACTGC ACAGCAATGC CAGTGAGTCC CTTGGAAAAG GCTACTCTGA TGGAGGGTGC 120  
TACGAGCAAC TTTTGTCTC TCCTGAGGTG TTTGTGACTC TGGGTGTCAT CAGCTTGTTG 180  
GAGAATATCT TAGTGATTGT GGCAATAGCC AAGAACAAGA ATCTGCATTC ACCCATGTAC 240  
30 TTTTTCATCT GCAGCTTGGC TGTGGCTGAT ATGCTGGTGA GCGTTTCAA TGGATCAGAA 300  
ACCATTATCA TCACCCATT AAACAGTACA GATACGGATG CACAGAGTTT CACAGTGAAT 360  
ATTGATAATG TCATTGACTC GGTGATCTGT AGCTCCTTGC TTGCATCCAT TTGCAGCCTG 420

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CTTCAATTG CAGTGGACAG GTACTTTACT ATCTTCTATG CTCTCCAGTA CCATAACATT 480  
 ATGACAGTTA AGCGGGTTGG GATCAGCATA AGTTGTATCT GGGCAGCTTG CACGGTTTCA 540  
 GGCATTTTGT TCATCATTTA CTCAGATAGT AGTGCTGTCA TCATCTGCCT CATCACCATG 600  
 TTCTTCACCA TGCTGGCTCT CATGGCTTCT CTCTATGTCC ACATGTTTCCT GATGGCCAGG 660  
 5 CTTACACATTA AGAGGATTGC TGTCCTCCCC GGCAGTGGTG CCATCCGCCA AGGTGCCAAT 720  
 ATGAAGGGAG CGATTACCTT GACCATCCTG ATTGGCGTCT TTGTTGTCTG CTGGGCCCCA 780  
 TTCTTCTCC ACTTAATATT CTACATCTCT TGTCTCAGA ATCCATATTG TGTGTGCTTC 840  
 ATGTCTCACT TTAACCTGTA TCTCATACTG ATCATGTGTA ATTCAATCAT CGATCCTCTG 900  
 ATTTATGCAC TCCGGAGTCA AGAACTGAGG AAAACCTTCA AAGAGATCAT CTGTTGCTAT 960  
 10 CCCCTGGGAG GCCTTTGTGA CTTGTCTAGC AGATATTAA 999

(75) INFORMATION FOR SEQ ID NO:74:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 332 amino acids  
 (B) TYPE: amino acid  
 15 (C) STRANDEDNESS:  
 (D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:74:

Met Val Asn Ser Thr His Arg Gly Met His Thr Ser Leu His Leu Trp  
 1 5 10 15  
 Asn Arg Ser Ser Tyr Arg Leu His Ser Asn Ala Ser Glu Ser Leu Gly  
 20 25 30  
 Lys Gly Tyr Ser Asp Gly Gly Cys Tyr Glu Gln Leu Phe Val Ser Pro  
 35 40 45  
 25 Glu Val Phe Val Thr Leu Gly Val Ile Ser Leu Leu Glu Asn Ile Leu  
 50 55 60  
 Val Ile Val Ala Ile Ala Lys Asn Lys Asn Leu His Ser Pro Met Tyr  
 65 70 75 80  
 Phe Phe Ile Cys Ser Leu Ala Val Ala Asp Met Leu Val Ser Val Ser  
 30 85 90 95  
 Asn Gly Ser Glu Thr Ile Ile Ile Thr Leu Leu Asn Ser Thr Asp Thr  
 100 105 110  
 Asp Ala Gln Ser Phe Thr Val Asn Ile Asp Asn Val Ile Asp Ser Val

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	115	120	125
	Ile Cys Ser Ser Leu Leu Ala Ser Ile Cys Ser Leu Leu Ser Ile Ala 130 135 140		
5	Val Asp Arg Tyr Phe Thr Ile Phe Tyr Ala Leu Gln Tyr His Asn Ile 145 150 155 160		
	Met Thr Val Lys Arg Val Gly Ile Ser Ile Ser Cys Ile Trp Ala Ala 165 170 175		
	Cys Thr Val Ser Gly Ile Leu Phe Ile Ile Tyr Ser Asp Ser Ser Ala 180 185 190		
10	Val Ile Ile Cys Leu Ile Thr Met Phe Phe Thr Met Leu Ala Leu Met 195 200 205		
	Ala Ser Leu Tyr Val His Met Phe Leu Met Ala Arg Leu His Ile Lys 210 215 220		
15	Arg Ile Ala Val Leu Pro Gly Thr Gly Ala Ile Arg Gln Gly Ala Asn 225 230 235 240		
	Met Lys Gly Ala Ile Thr Leu Thr Ile Leu Ile Gly Val Phe Val Val 245 250 255		
	Cys Trp Ala Pro Phe Phe Leu His Leu Ile Phe Tyr Ile Ser Cys Pro 260 265 270		
20	Gln Asn Pro Tyr Cys Val Cys Phe Met Ser His Phe Asn Leu Tyr Leu 275 280 285		
	Ile Leu Ile Met Cys Asn Ser Ile Ile Asp Pro Leu Ile Tyr Ala Leu 290 295 300		
25	Arg Ser Gln Glu Leu Arg Lys Thr Phe Lys Glu Ile Ile Cys Cys Tyr 305 310 315 320		
	Pro Leu Gly Gly Leu Cys Asp Leu Ser Ser Arg Tyr 325 330		

(76) INFORMATION FOR SEQ ID NO:75:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 32 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA (genomic)

- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:75:

CCGAAGCTTC GAGCTGAGTA AGGCGGCGGG CT

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(77) INFORMATION FOR SEQ ID NO:76:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 31 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

5

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:76:

GTGGAATTCA TTTGCCCTGC CTCAACCCCC A

31

10 (78) INFORMATION FOR SEQ ID NO:77:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 1344 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

15

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:77:

ATGGAGCTGC TAAAGCTGAA CCGGAGCGTG CAGGGAACCG GACCCGGGCC GGGGGCTTCC 60  
CTGTGCCGCC CGGGGGCGCC TCTCCTCAAC AGCAGCAGTG TGGGCAACCT CAGCTGCGAG 120  
20 CCCCCTCGCA TTCGCGGAGC CGGGACACGA GAATTGGAGC TGGCCATTAG AATCACTCTT 180  
TACGCAGTGA TCTTCCTGAT GAGCGTTGGA GGAAATATGC TCATCATCGT GGTCTTGGGA 240  
CTGAGCCGCC GCCTGAGGAC TGTCACCAAT GCCTTCCTCC TCTCACTGGC AGTCAGCGAC 300  
CTCCTGCTGG CTGTGGCTTG CATGCCCTTC ACCCTCCTGC CCAATCTCAT GGGCACATTC 360  
ATCTTTGGCA CCGTCATCTG CAAGGCGGTT TCCTACCTCA TGGGGGTGTC TGTGAGTGTG 420  
25 TCCACGCTAA GCCTCGTGGC CATCGCACTG GAGCGATATA GCGCCATCTG CCGACCACTG 480  
CAGGCACGAG TGTGGCAGAC GCGCTCCAC GCGGCTCGCG TGATTGTAGC CACGTGGCTG 540  
CTGTCCGGAC TACTCATGGT GCCCTACCCC GTGTACACTG TCGTGCAACC AGTGGGGCCT 600  
CGTGTGCTGC AGTGCGTGCA TCGCTGGCCC AGTGCGCGGG TCCGCCAGAC CTGGTCCGTA 660  
CTGCTGCTTC TGCTCTTGTT CTTCATCCCA GGTGTGGTTA TGGCCGTGGC CTACGGGCTT 720  
30 ATCTCTCGCG AGCTCTACTT AGGGCTTCGC TTTGACGGCG ACAGTGACAG CGACAGCCAA 780  
AGCAGGGTCC GAAACCAAGG CGGGCTGCCA GGGGCTGTTC ACCAGAACGG GCGTTGCCGG 840

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CCTGAGACTG GCGCGGTTGG CAAAGACAGC GATGGCTGCT ACGTGCAACT TCCACGTTCC 900  
 CGGCCTGCCC TGGAGCTGAC GGCCTGACG GCTCCTGGGC CGGGATCCGG CTCCCGGCCC 960  
 ACCCAGGCCA AGCTGCTGGC TAAGAAGCGC GTGGTGCGAA TGTGCTGGT GATCGTTGTG 1020  
 CTTTTTTTTC TGTGTTGGTT GCCAGTTTAT AGTGCCAACA CGTGGCGCGC CTTTGATGGC 1080  
 5 CCGGGTGAC ACCGAGCACT CTCGGGTGCT CCTATCTCCT TCATTCACTT GCTGAGCTAC 1140  
 GCCTCGGCCT GTGTCAACCC CCTGGTCTAC TGCTTCATGC ACCGTCGCTT TCGCCAGGCC 1200  
 TGCCTGGAAA CTTGCGCTCG CTGCTGCCCC CGGCCTCCAC GAGCTCGCCC CAGGGCTCTT 1260  
 CCCGATGAGG ACCCTCCCAC TCCCTCCATT GCTTCGCTGT CCAGGCTTAG CTACACCACC 1320  
 ATCAGCACAC TGGGCCCTGG CTGA 1344

10 (79) INFORMATION FOR SEQ ID NO:78:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 447 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - 15 (D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:78:

Met Glu Leu Leu Lys Leu Asn Arg Ser Val Gln Gly Thr Gly Pro Gly  
 1 5 10 15  
 20 Pro Gly Ala Ser Leu Cys Arg Pro Gly Ala Pro Leu Leu Asn Ser Ser  
 20 25 30  
 Ser Val Gly Asn Leu Ser Cys Glu Pro Pro Arg Ile Arg Gly Ala Gly  
 35 40 45  
 25 Thr Arg Glu Leu Glu Leu Ala Ile Arg Ile Thr Leu Tyr Ala Val Ile  
 50 55 60  
 Phe Leu Met Ser Val Gly Gly Asn Met Leu Ile Ile Val Val Leu Gly  
 65 70 75 80  
 Leu Ser Arg Arg Leu Arg Thr Val Thr Asn Ala Phe Leu Leu Ser Leu  
 85 90 95  
 30 Ala Val Ser Asp Leu Leu Leu Ala Val Ala Cys Met Pro Phe Thr Leu  
 100 105 110  
 Leu Pro Asn Leu Met Gly Thr Phe Ile Phe Gly Thr Val Ile Cys Lys  
 115 120 125

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Ala Val Ser Tyr Leu Met Gly Val Ser Val Ser Val Ser Thr Leu Ser  
 130 135 140  
 Leu Val Ala Ile Ala Leu Glu Arg Tyr Ser Ala Ile Cys Arg Pro Leu  
 145 150 155 160  
 5 Gln Ala Arg Val Trp Gln Thr Arg Ser His Ala Ala Arg Val Ile Val  
 165 170 175  
 Ala Thr Trp Leu Leu Ser Gly Leu Leu Met Val Pro Tyr Pro Val Tyr  
 180 185 190  
 10 Thr Val Val Gln Pro Val Gly Pro Arg Val Leu Gln Cys Val His Arg  
 195 200 205  
 Trp Pro Ser Ala Arg Val Arg Gln Thr Trp Ser Val Leu Leu Leu Leu  
 210 215 220  
 Leu Leu Phe Phe Ile Pro Gly Val Val Met Ala Val Ala Tyr Gly Leu  
 225 230 235 240  
 15 Ile Ser Arg Glu Leu Tyr Leu Gly Leu Arg Phe Asp Gly Asp Ser Asp  
 245 250 255  
 Ser Asp Ser Gln Ser Arg Val Arg Asn Gln Gly Gly Leu Pro Gly Ala  
 260 265 270  
 20 Val His Gln Asn Gly Arg Cys Arg Pro Glu Thr Gly Ala Val Gly Lys  
 275 280 285  
 Asp Ser Asp Gly Cys Tyr Val Gln Leu Pro Arg Ser Arg Pro Ala Leu  
 290 295 300  
 Glu Leu Thr Ala Leu Thr Ala Pro Gly Pro Gly Ser Gly Ser Arg Pro  
 305 310 315 320  
 25 Thr Gln Ala Lys Leu Leu Ala Lys Lys Arg Val Val Arg Met Leu Leu  
 325 330 335  
 Val Ile Val Val Leu Phe Phe Leu Cys Trp Leu Pro Val Tyr Ser Ala  
 340 345 350  
 30 Asn Thr Trp Arg Ala Phe Asp Gly Pro Gly Ala His Arg Ala Leu Ser  
 355 360 365  
 Val Ala Pro Ile Ser Phe Ile His Leu Leu Ser Tyr Ala Ser Ala Cys  
 370 375 380  
 Val Asn Pro Leu Val Tyr Cys Phe Met His Arg Arg Phe Arg Gln Ala  
 385 390 395 400  
 35 Cys Leu Glu Thr Cys Ala Arg Cys Cys Pro Arg Pro Pro Arg Ala Arg  
 405 410 415  
 Pro Arg Ala Leu Pro Asp Glu Asp Pro Pro Thr Pro Ser Ile Ala Ser

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420

425

430

Leu Ser Arg Leu Ser Tyr Thr Thr Ile Ser Thr Leu Gly Pro Gly  
435 440 445

(80) INFORMATION FOR SEQ ID NO:79:

- 5 (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 30 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear
- 10 (ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:79:

TGCAAGCTTA AAAAGGAAAA AATGAACAGC

30

(81) INFORMATION FOR SEQ ID NO:80:

- 15 (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 30 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA (genomic)

20 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:80:

TAAGGATCCC TTCCCTTCAA AACATCCTTG

30

(82) INFORMATION FOR SEQ ID NO:81:

- 25 (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 1014 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:81:

30 ATGAACAGCA CATGTATTGA AGAACAGCAT GACCTGGATC ACTATTTGTT TCCCATTGTT 60  
TACATCTTTG TGATTATAGT CAGCATTCCA GCCAATATTG GATCTCTGTG TGTGTCTTTC 120  
CTGCAACCCA AGAAGGAAAG TGAAC TAGGA ATTTACCTCT TCAGTTTGTC ACTATCAGAT 180  
TTACTCTATG CATTA ACTCT CCCTTTATGG ATTGATTATA CTTGGAATAA AGACAACTGG 240



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ACTTTCTCTC CTGCCTTGTG CAAAGGGAGT GCTTTTCTCA TGTACATGAA GTTTTACAGC 300  
 AGCACAGCAT TCCTCACCTG CATTGCCGTT GATCGGTATT TGGCTGTTGT CTACCCTTTG 360  
 AAGTTTTTTT TCCTAAGGAC AAGAAGAATT GCACTCATGG TCAGCCTGTC CATCTGGATA 420  
 TTGGAAACCA TCTTCAATGC TGTCATGTTG TGGGAAGATG AAACAGTTGT TGAATATTGC 480  
 5 GATGCCGAAA AGTCTAATTT TACTTTATGC TATGACAAAT ACCCTTTAGA GAAATGGCAA 540  
 ATCAACCTCA ACTTGTTTCTG GACGTGTACA GGCTATGCAA TACCTTTGGT CACCATCCTG 600  
 ATCTGTAACC GGAAAGTCTA CCAAGCTGTG CGGCACAATA AAGCCACGGA AAACAAGGAA 660  
 AAGAAGAGAA TCATAAAACT ACTTGTCAGC ATCACAGTTA CTTTGTCTT ATGCTTTACT 720  
 CCCTTTCATG TGATGTTGCT GATTCGCTGC ATTTTAGAGC ATGCTGTGAA CTTGGAAGAC 780  
 10 CACAGCAATT CTGGGAAGCG AACTTACACA ATGTATAGAA TCACGGTTGC ATTAACAAGT 840  
 TTAAATGTG TTGCTGATCC AATTCTGTAC TGTTTTGTTA CCGAAACAGG AAGATATGAT 900  
 ATGTGGAATA TATTAAATTT CTGCACTGGG AGGTGTAATA CATCACAAAG ACAAAGAAAA 960  
 CGCATACTTT CTGTGTCTAC AAAAGATACT ATGGAATTAG AGGTCCTTGA GTAG 1014

(83) INFORMATION FOR SEQ ID NO:82:

- 15 (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 337 amino acids  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS:  
 (D) TOPOLOGY: not relevant

20 (ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:82:

Met Asn Ser Thr Cys Ile Glu Glu Gln His Asp Leu Asp His Tyr Leu  
 1 5 10 15  
 Phe Pro Ile Val Tyr Ile Phe Val Ile Ile Val Ser Ile Pro Ala Asn  
 25 20 25 30  
 Ile Gly Ser Leu Cys Val Ser Phe Leu Gln Pro Lys Lys Glu Ser Glu  
 35 40 45  
 Leu Gly Ile Tyr Leu Phe Ser Leu Ser Leu Ser Asp Leu Leu Tyr Ala  
 50 55 60  
 30 Leu Thr Leu Pro Leu Trp Ile Asp Tyr Thr Trp Asn Lys Asp Asn Trp  
 65 70 75 80  
 Thr Phe Ser Pro Ala Leu Cys Lys Gly Ser Ala Phe Leu Met Tyr Met

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	85	90	95
	Lys Phe Tyr Ser Ser Thr Ala Phe Leu Thr Cys Ile Ala Val Asp Arg		
	100	105	110
5	Tyr Leu Ala Val Val Tyr Pro Leu Lys Phe Phe Phe Leu Arg Thr Arg		
	115	120	125
	Arg Ile Ala Leu Met Val Ser Leu Ser Ile Trp Ile Leu Glu Thr Ile		
	130	135	140
	Phe Asn Ala Val Met Leu Trp Glu Asp Glu Thr Val Val Glu Tyr Cys		
	145	150	155
10	Asp Ala Glu Lys Ser Asn Phe Thr Leu Cys Tyr Asp Lys Tyr Pro Leu		
	165	170	175
	Glu Lys Trp Gln Ile Asn Leu Asn Leu Phe Arg Thr Cys Thr Gly Tyr		
	180	185	190
15	Ala Ile Pro Leu Val Thr Ile Leu Ile Cys Asn Arg Lys Val Tyr Gln		
	195	200	205
	Ala Val Arg His Asn Lys Ala Thr Glu Asn Lys Glu Lys Lys Arg Ile		
	210	215	220
	Ile Lys Leu Leu Val Ser Ile Thr Val Thr Phe Val Leu Cys Phe Thr		
	225	230	235
20	Pro Phe His Val Met Leu Leu Ile Arg Cys Ile Leu Glu His Ala Val		
	245	250	255
	Asn Phe Glu Asp His Ser Asn Ser Gly Lys Arg Thr Tyr Thr Met Tyr		
	260	265	270
25	Arg Ile Thr Val Ala Leu Thr Ser Leu Asn Cys Val Ala Asp Pro Ile		
	275	280	285
	Leu Tyr Cys Phe Val Thr Glu Thr Gly Arg Tyr Asp Met Trp Asn Ile		
	290	295	300
	Leu Lys Phe Cys Thr Gly Arg Cys Asn Thr Ser Gln Arg Gln Arg Lys		
	305	310	315
30	Arg Ile Leu Ser Val Ser Thr Lys Asp Thr Met Glu Leu Glu Val Leu		
	325	330	335
	Glu		

(84) INFORMATION FOR SEQ ID NO:83:

- 35 (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 40 base pairs  
 (B) TYPE: nucleic acid

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(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:83:

5 CAGGAAGAAG AAACGAGCTG TCATTATGAT GGTGACAGTG  
40

(85) INFORMATION FOR SEQ ID NO:84:

(i) SEQUENCE CHARACTERISTICS:

10 (A) LENGTH: 40 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:84:

15 CACTGTCACC ATCATAATGA CAGCTCGTTT CTTCTTCCTG  
40

(86) INFORMATION FOR SEQ ID NO:85:

(i) SEQUENCE CHARACTERISTICS:

20 (A) LENGTH: 30 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:85:

25 GGCCACCGGC AGACCAAACG CGTCCTGCTG  
30

(87) INFORMATION FOR SEQ ID NO:86:

(i) SEQUENCE CHARACTERISTICS:

30 (A) LENGTH: 31 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:86:

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CTCCTTCGGT CCTCCTATCG TTGTCAGAAG T  
31

(88) INFORMATION FOR SEQ ID NO:87:

- 5 (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 37 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

10 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:87:

GGAAAAGAAG AGAATCAAAA AACTACTTGT CAGCATC

37

(89) INFORMATION FOR SEQ ID NO:88:

- 15 (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 31 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:88:

20 CTCCTTCGGT CCTCCTATCG TTGTCAGAAG T

31

(90) INFORMATION FOR SEQ ID NO:89:

- 25 (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 1080 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:89:

ATGATTCTCA ACTCTTCTAC TGAAGATGGT ATTAAAAGAA TCCAAGATGA TTGTCCCAAA 60

30 GCTGGAAGGC ATAATTACAT ATTTGTCATG ATTCCTACTT TATACAGTAT CATCTTTGTG 120

GTGGGAATAT TTGGAAACAG CTTGGTGGTG ATAGTCATTT ACTTTTATAT GAAGCTGAAG 180

ACTGTGGCCA GTGTTTTTCT TTTGAATTTA GCACTGGCTG ACTTATGCTT TTTACTGACT 240

TTGCCACTAT GGGCTGTCTA CACAGCTATG GAATACCGCT GGCCCTTTGG CAATTACCTA 300

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TGTAAGATTG CTTCAGCCAG CGTCAGTTTC AACCTGTACG CTAGTGTGTT TCTACTCAGC 360  
 TGTCTCAGCA TTGATCGATA CCTGGCTATT GTTCACCCAA TGAAGTCCCG CCTTCGACGC 420  
 ACAATGCTTG TAGCCAAAGT CACCTGCATC ATCATTGGC TGCTGGCAGG CTTGGCCAGT 480  
 TTGCCAGCTA TAATCCATCG AAATGTATTT TTCATTGAGA ACACCAATAT TACAGTTTGT 540  
 5 GCTTTCCATT ATGAGTCCCA AAATTCAACC CTTCCGATAG GGCTGGGCCT GACCAAAAAT 600  
 ATACTGGGTT TCCTGTTTCC TTTTCTGATC ATTCTTACAA GTTATACTCT TATTTGGAAG 660  
 GCCCTAAAGA AGGCTTATGA AATTCAGAAG AACAAACCAA GAAATGATGA TATTAAAAAG 720  
 ATAATTATGG CAATTGTGCT TTTCTTTTTC TTTTCTGGA TTCCCCACCA AATATTCACT 780  
 TTTCTGGATG TATTGATTCA ACTAGGCATC ATACGTGACT GTAGAATTGC AGATATTGTG 840  
 10 GACACGGCCA TGCCTATCAC CATTTGTATA GCTTATTTTA ACAATTGCCT GAATCCTCTT 900  
 TTTTATGGCT TTCTGGGGAA AAAATTTAAA AGATATTTTC TCCAGCTTCT AAAATATATT 960  
 CCCCCAAAAG CCAAATCCCA CTCAAACCTT TCAACAAAAA TGAGCACGCT TTCCTACCGC 1020  
 CCCTCAGATA ATGTAAGCTC ATCCACCAAG AAGCCTGCAC CATGTTTTGA GGTGAGTGA 1080

(91) INFORMATION FOR SEQ ID NO:90:

- 15 (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 359 amino acids  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS:  
 (D) TOPOLOGY: not relevant

- 20 (ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:90:

Met Ile Leu Asn Ser Ser Thr Glu Asp Gly Ile Lys Arg Ile Gln Asp  
 1 5 10 15  
 Asp Cys Pro Lys Ala Gly Arg His Asn Tyr Ile Phe Val Met Ile Pro  
 25 20 25 30  
 Thr Leu Tyr Ser Ile Ile Phe Val Val Gly Ile Phe Gly Asn Ser Leu  
 35 40 45  
 Val Val Ile Val Ile Tyr Phe Tyr Met Lys Leu Lys Thr Val Ala Ser  
 50 55 60  
 30 Val Phe Leu Leu Asn Leu Ala Leu Ala Asp Leu Cys Phe Leu Leu Thr  
 65 70 75 80  
 Leu Pro Leu Trp Ala Val Tyr Thr Ala Met Glu Tyr Arg Trp Pro Phe

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	85	90	95
	Gly Asn Tyr Leu Cys Lys Ile Ala Ser Ala Ser Val Ser Phe Asn Leu 100 105 110		
5	Tyr Ala Ser Val Phe Leu Leu Thr Cys Leu Ser Ile Asp Arg Tyr Leu 115 120 125		
	Ala Ile Val His Pro Met Lys Ser Arg Leu Arg Arg Thr Met Leu Val 130 135 140		
	Ala Lys Val Thr Cys Ile Ile Ile Trp Leu Leu Ala Gly Leu Ala Ser 145 150 155 160		
10	Leu Pro Ala Ile Ile His Arg Asn Val Phe Phe Ile Glu Asn Thr Asn 165 170 175		
	Ile Thr Val Cys Ala Phe His Tyr Glu Ser Gln Asn Ser Thr Leu Pro 180 185 190		
15	Ile Gly Leu Gly Leu Thr Lys Asn Ile Leu Gly Phe Leu Phe Pro Phe 195 200 205		
	Leu Ile Ile Leu Thr Ser Tyr Thr Leu Ile Trp Lys Ala Leu Lys Lys 210 215 220		
	Ala Tyr Glu Ile Gln Lys Asn Lys Pro Arg Asn Asp Asp Ile Lys Lys 225 230 235 240		
20	Ile Ile Met Ala Ile Val Leu Phe Phe Phe Phe Ser Trp Ile Pro His 245 250 255		
	Gln Ile Phe Thr Phe Leu Asp Val Leu Ile Gln Leu Gly Ile Ile Arg 260 265 270		
25	Asp Cys Arg Ile Ala Asp Ile Val Asp Thr Ala Met Pro Ile Thr Ile 275 280 285		
	Cys Ile Ala Tyr Phe Asn Asn Cys Leu Asn Pro Leu Phe Tyr Gly Phe 290 295 300		
	Leu Gly Lys Lys Phe Lys Arg Tyr Phe Leu Gln Leu Leu Lys Tyr Ile 305 310 315 320		
30	Pro Pro Lys Ala Lys Ser His Ser Asn Leu Ser Thr Lys Met Ser Thr 325 330 335		
	Leu Ser Tyr Arg Pro Ser Asp Asn Val Ser Ser Ser Thr Lys Lys Pro 340 345 350		
35	Ala Pro Cys Phe Glu Val Glu 355		

(92) INFORMATION FOR SEQ ID NO:91:

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- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 35 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

5

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:91:

CCAAGAAATG ATGATATTAA AAAGATAATT ATGGC

35

(93) INFORMATION FOR SEQ ID NO:92:

- 10 (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 31 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

15 (ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:92:

CTCCTTCGGT CCTCCTATCG TTGTCAGAAG T

31

(94) INFORMATION FOR SEQ ID NO:93:

- 20 (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 1080 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

25 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:93:

ATGATTCTCA ACTCTTCTAC TGAAGATGGT ATTAAAAGAA TCCAAGATGA TTGTCCCAAA 60  
GCTGGAAGGC ATAATTACAT ATTTGTCATG ATTCCTACTT TATACAGTAT CATCTTTGTG 120  
GTGGGAATAT TTGGAAACAG CTTGGTGGTG ATAGTCATTT ACTTTTATAT GAAGCTGAAG 180  
ACTGTGGCCA GTGTTTTTCT TTTGAATTTA GCACTGGCTG ACTTATGCTT TTTACTGACT 240  
30 TTGCCACTAT GGGCTGTCTA CACAGCTATG GAATACCGCT GGCCCTTTGG CAATTACCTA 300  
TGTAAGATTG CTTCAGCCAG CGTCAGTTTC GCCCTGTACG CTAGTGTGTT TCTACTCAGC 360  
TGTCTCAGCA TTGATCGATA CCTGGCTATT GTTCACCCAA TGAAGTCCCG CCTTCGACGC 420

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ACAATGCTTG TAGCCAAAGT CACCTGCATC ATCATTTGGC TGCTGGCAGG CTTGGCCAGT 480  
 TTGCCAGCTA TAATCCATCG AAATGTATTT TTCATTGAGA ACACCAATAT TACAGTTTGT 540  
 GCTTTCCATT ATGAGTCCCA AAATTCAACC CTTCCGATAG GGCTGGGCCT GACCAAAAAT 600  
 AACTGGGTT TCCTGTTTCC TTTTCTGATC ATTCTTACAA GTTATACTCT TATTTGGAAG 660  
 5 GCCCTAAAGA AGGCTTATGA AATTCAGAAG AACAAACCAA GAAATGATGA TATTTTAAAG 720  
 ATAATTATGG CAATTGTGCT TTTCTTTTTC TTTTCTGGA TTCCCCACCA AATATTCAT 780  
 TTTCTGGATG TATTGATTCA ACTAGGCATC ATACGTGACT GTAGAATTGC AGATATTGTG 840  
 GACACGGCCA TGCCTATCAC CATTGTATA GCTTATTTTA ACAATTGCCT GAATCCTCTT 900  
 TTTTATGGCT TTCTGGGGAA AAAATTTAAA AGATATTTTC TCCAGCTTCT AAAATATATT 960  
 10 CCCCCAAAAG CCAAATCCCA CTCAAACCTT TCAACAAAAA TGAGCACGCT TTCCTACCGC 1020  
 CCCTCAGATA ATGTAAGCTC ATCCACCAAG AAGCCTGCAC CATGTTTTGA GGTGAGTGA 1080

(95) INFORMATION FOR SEQ ID NO:94:

(i) SEQUENCE CHARACTERISTICS:

- 15 (A) LENGTH: 359 amino acids  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS:  
 (D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:94:

20 Met Ile Leu Asn Ser Ser Thr Glu Asp Gly Ile Lys Arg Ile Gln Asp  
 1 5 10 15  
 Asp Cys Pro Lys Ala Gly Arg His Asn Tyr Ile Phe Val Met Ile Pro  
 20 25 30  
 25 Thr Leu Tyr Ser Ile Ile Phe Val Val Gly Ile Phe Gly Asn Ser Leu  
 35 40 45  
 Val Val Ile Val Ile Tyr Phe Tyr Met Lys Leu Lys Thr Val Ala Ser  
 50 55 60  
 Val Phe Leu Leu Asn Leu Ala Leu Ala Asp Leu Cys Phe Leu Leu Thr  
 65 70 75 80  
 30 Leu Pro Leu Trp Ala Val Tyr Thr Ala Met Glu Tyr Arg Trp Pro Phe  
 85 90 95  
 Gly Asn Tyr Leu Cys Lys Ile Ala Ser Ala Ser Val Ser Phe Ala Leu



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	100	105	110
	Tyr Ala Ser Val Phe Leu Leu Thr Cys Leu Ser Ile Asp Arg Tyr Leu		
	115	120	125
5	Ala Ile Val His Pro Met Lys Ser Arg Leu Arg Arg Thr Met Leu Val		
	130	135	140
	Ala Lys Val Thr Cys Ile Ile Ile Trp Leu Leu Ala Gly Leu Ala Ser		
	145	150	155 160
	Leu Pro Ala Ile Ile His Arg Asn Val Phe Phe Ile Glu Asn Thr Asn		
		165	170 175
10	Ile Thr Val Cys Ala Phe His Tyr Glu Ser Gln Asn Ser Thr Leu Pro		
	180	185	190
	Ile Gly Leu Gly Leu Thr Lys Asn Ile Leu Gly Phe Leu Phe Pro Phe		
	195	200	205
15	Leu Ile Ile Leu Thr Ser Tyr Thr Leu Ile Trp Lys Ala Leu Lys Lys		
	210	215	220
	Ala Tyr Glu Ile Gln Lys Asn Lys Pro Arg Asn Asp Asp Ile Phe Lys		
	225	230	235 240
	Ile Ile Met Ala Ile Val Leu Phe Phe Phe Phe Ser Trp Ile Pro His		
		245	250 255
20	Gln Ile Phe Thr Phe Leu Asp Val Leu Ile Gln Leu Gly Ile Ile Arg		
	260	265	270
	Asp Cys Arg Ile Ala Asp Ile Val Asp Thr Ala Met Pro Ile Thr Ile		
	275	280	285
25	Cys Ile Ala Tyr Phe Asn Asn Cys Leu Asn Pro Leu Phe Tyr Gly Phe		
	290	295	300
	Leu Gly Lys Lys Phe Lys Arg Tyr Phe Leu Gln Leu Leu Lys Tyr Ile		
	305	310	315 320
	Pro Pro Lys Ala Lys Ser His Ser Asn Leu Ser Thr Lys Met Ser Thr		
		325	330 335
30	Leu Ser Tyr Arg Pro Ser Asp Asn Val Ser Ser Ser Thr Lys Lys Pro		
	340	345	350
	Ala Pro Cys Phe Glu Val Glu		
	355		

(97) INFORMATION FOR SEQ ID NO:95:

- 35 (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 26 base pairs  
 (B) TYPE: nucleic acid

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(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iv) ANTI-SENSE: NO

5 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:95:

CCCAAGCTTC CCCAGGTGTA TTGAT

26

(97) INFORMATION FOR SEQ ID NO:96:

(i) SEQUENCE CHARACTERISTICS:

10 (A) LENGTH: 29 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iv) ANTI-SENSE: YES

15 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:96:

CCTGCAGGCG AAAGTGACTC TGGCTGAAG

29

(98) INFORMATION FOR SEQ ID NO:97:

(i) SEQUENCE CHARACTERISTICS:

20 (A) LENGTH: 42 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iv) ANTI-SENSE: NO

25 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:97:

CTGTACGCTA GTGTGTTTCT ACTCACGTGT CTCAGCATTG AT

42

(99) INFORMATION FOR SEQ ID NO:98:

(i) SEQUENCE CHARACTERISTICS:

30 (A) LENGTH: 26 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

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(iv) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:98:

GTTGGATCCA CATAATGCAT TTTCTC

26

(100) INFORMATION FOR SEQ ID NO:99:

- 5 (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 1080 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

10 (ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:99:

ATGATTCTCA ACTCTTCTAC TGAAGATGGT ATTAAGAGAA TCCAAGATGA TTGTCCCAAA 60  
GCTGGAAGGC ATAATTACAT ATTTGTCATG ATTCCTACTT TATACAGTAT CATCTTTGTG 120  
GTGGGAATAT TTGGAAACAG CTTGGTGGTG ATAGTCATTT ACTTTTATAT GAAGCTGAAG 180  
15 ACTGTGGCCA GTGTTTTTCT TTTGAATTTA GCACTGGCTG ACTTATGCTT TTTACTGACT 240  
TTGCCACTAT GGGCTGTCTA CACAGCTATG GAATACCGCT GGCCCTTTGG CAATTACCTA 300  
TGTAAGATTG CTTCAGCCAG CGTCAGTTTC AACCTGTACG CTAGTGTGTT TCTACTCAG 360  
TGTCTCAGCA TTGATCGATA CCTGGCTATT GTTCACCCAA TGAAGTCCCG CCTTCGACGC 420  
ACAATGCTTG TAGCCAAAGT CACCTGCATC ATCATTGCGC TGCTGGCAGG CTGGCCAGT 480  
20 TTGCCAGCTA TAATCCATCG AAATGTATTT TTCATTGAGA ACACCAATAT TACAGTTTGT 540  
GCTTTCCATT ATGAGTCCCA AAATCAACC CTTCCGATAG GGCTGGGCCT GACCAAAAAAT 600  
ATACTGGGTT TCCTGTTTCC TTTTCTGATC ATTCTTACAA GTTATTTTGG AATTCGAAAA 660  
CACTTACTGA AGACGAATAG CTATGGGAAG AACAGGATAA CCCGTGACCA AGTTAAGAAG 720  
ATAATTATGG CAATTGTGCT TTTCTTTTTC TTTTCTGGA TTCCCCACCA AATATTCCT 780  
25 TTTCTGGATG TATTGATTCA ACTAGGCATC ATACGTGACT GTAGAATTGC AGATATTGTG 840  
GACACGGCCA TGCCTATCAC CATTTGTATA GCTTATTTTA ACAATTGCCT GAATCCTCTT 900  
TTTTATGGCT TTCTGGGGAA AAAATTTAAA AGATATTTTC TCCAGCTTCT AAAATATATT 960  
CCCCCAAAG CCAAATCCCA CTCAAACCTT TCAACAAAAA TGAGCAGCT TTCCTACCGC 1020  
CCCTCAGATA ATGTAAGCTC ATCCACCAAG AAGCCTGCAC CATGTTTTGA GGTGAGTGA 1080

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(101) INFORMATION FOR SEQ ID NO:100:

## (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 359 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:100:

10	Met	Ile	Leu	Asn	Ser	Ser	Thr	Glu	Asp	Gly	Ile	Lys	Arg	Ile	Gln	Asp	1	5	10	15
	Asp	Cys	Pro	Lys	Ala	Gly	Arg	His	Asn	Tyr	Ile	Phe	Val	Met	Ile	Pro	20	25	30	
	Thr	Leu	Tyr	Ser	Ile	Ile	Phe	Val	Val	Gly	Ile	Phe	Gly	Asn	Ser	Leu	35	40	45	
15	Val	Val	Ile	Val	Ile	Tyr	Phe	Tyr	Met	Lys	Leu	Lys	Thr	Val	Ala	Ser	50	55	60	
	Val	Phe	Leu	Leu	Asn	Leu	Ala	Leu	Ala	Asp	Leu	Cys	Phe	Leu	Leu	Thr	65	70	75	80
20	Leu	Pro	Leu	Trp	Ala	Val	Tyr	Thr	Ala	Met	Glu	Tyr	Arg	Trp	Pro	Phe	85	90	95	
	Gly	Asn	Tyr	Leu	Cys	Lys	Ile	Ala	Ser	Ala	Ser	Val	Ser	Phe	Asn	Leu	100	105	110	
	Tyr	Ala	Ser	Val	Phe	Leu	Leu	Thr	Cys	Leu	Ser	Ile	Asp	Arg	Tyr	Leu	115	120	125	
25	Ala	Ile	Val	His	Pro	Met	Lys	Ser	Arg	Leu	Arg	Arg	Thr	Met	Leu	Val	130	135	140	
	Ala	Lys	Val	Thr	Cys	Ile	Ile	Ile	Trp	Leu	Leu	Ala	Gly	Leu	Ala	Ser	145	150	155	160
30	Leu	Pro	Ala	Ile	Ile	His	Arg	Asn	Val	Phe	Phe	Ile	Glu	Asn	Thr	Asn	165	170	175	
	Ile	Thr	Val	Cys	Ala	Phe	His	Tyr	Glu	Ser	Gln	Asn	Ser	Thr	Leu	Pro	180	185	190	
	Ile	Gly	Leu	Gly	Leu	Thr	Lys	Asn	Ile	Leu	Gly	Phe	Leu	Phe	Pro	Phe	195	200	205	
35	Leu	Ile	Ile	Leu	Thr	Ser	Tyr	Phe	Gly	Ile	Arg	Lys	His	Leu	Leu	Lys	210	215	220	

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Thr Asn Ser Tyr Gly Lys Asn Arg Ile Thr Arg Asp Gln Val Lys Lys  
 225 230 235 240  
 Ile Ile Met Ala Ile Val Leu Phe Phe Phe Phe Ser Trp Ile Pro His  
 245 250 255  
 5 Gln Ile Phe Thr Phe Leu Asp Val Leu Ile Gln Leu Gly Ile Ile Arg  
 260 265 270  
 Asp Cys Arg Ile Ala Asp Ile Val Asp Thr Ala Met Pro Ile Thr Ile  
 275 280 285  
 10 Cys Ile Ala Tyr Phe Asn Asn Cys Leu Asn Pro Leu Phe Tyr Gly Phe  
 290 295 300  
 Leu Gly Lys Lys Phe Lys Arg Tyr Phe Leu Gln Leu Leu Lys Tyr Ile  
 305 310 315 320  
 Pro Pro Lys Ala Lys Ser His Ser Asn Leu Ser Thr Lys Met Ser Thr  
 325 330 335  
 15 Leu Ser Tyr Arg Pro Ser Asp Asn Val Ser Ser Ser Thr Lys Lys Pro  
 340 345 350  
 Ala Pro Cys Phe Glu Val Glu  
 355

## (102) INFORMATION FOR SEQ ID NO:101:

- 20 (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 37 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear  
 25 (ii) MOLECULE TYPE: DNA (genomic)  
 (iv) ANTI-SENSE: YES

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:101:

TCCGAATTCC AAAATAACTT GTAAGAATGA TCAGAAA

37

## (103) INFORMATION FOR SEQ ID NO:102:

- 30 (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 33 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear  
 35 (ii) MOLECULE TYPE: DNA (genomic)  
 (iv) ANTI-SENSE: NO

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:102:

AGATCTTAAG AAGATAATTA TGGCAATTGT GCT

33

(104) INFORMATION FOR SEQ ID NO:103:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 62 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

10 (iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:103:

AATTCGAAAA CACTTACTGA AGACGAATAG CTATGGGAAG AACAGGATAA CCCGTGACCA 60

AG

62

(105) INFORMATION FOR SEQ ID NO:104:

- 15 (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 62 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

20 (ii) MOLECULE TYPE: DNA (genomic)

(iv) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:104:

TTAACTTGGT CACGGGTTAT CCTGTTCTTC CCATAGCTAT TCGTCTTCAG TAAGTGTTTT 60

CG

62

25 (106) INFORMATION FOR SEQ ID NO:105:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 1083 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

30

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:105:

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ATGATTCTCA ACTCTTCTAC TGAAGATGGT ATTAAGAGAA TCCAAGATGA TTGTCCCAAA 60  
GCTGGAAGGC ATAATTACAT ATTTGTCATG ATTCCTACTT TATACAGTAT CATCTTTGTG 120  
GTGGGAATAT TTGGAAACAG CTTGGTGGTG ATAGTCATTT ACTTTTATAT GAAGCTGAAG 180  
ACTGTGGCCA GTGTTTTTCT TTTGAATTGA GCACTGGCTG ACTTATGCTT TTTACTGACT 240  
5 TTGCCACTAT GGGCTGTCTA CACAGCTATG GAATACCGCT GGCCCTTTGG CAATTACCTA 300  
TGTAAGATTG CTTAGCCAG CGTCAGTTT AACCTGTACG CTAGTGTGTT TCTACTCAGC 360  
TGTCTCAGCA TTGATCGATA CCTGGCTATT GTTCACCCAA TGAAGTCCCG CCTTCGACGC 420  
ACAATGCTTG TAGCCAAAGT CACCTGCATC ATCATTGTCG TGCTGGCAGG CTTGGCCAGT 480  
TTGCCAGCTA TAATCCATCG AAATGTATTT TTCATTGAGA ACACCAATAT TACAGTTTGT 540  
10 GCTTTCCATT ATGAGTCCCA AAATTCAACC CTTCCGATAG GGCTGGGCCT GACCAAAAAT 600  
ATACTGGGTT TCCTGTTTCC TTTTCTGATC ATTCTTACAA GTTATACTCT TATTTGGAAG 660  
GCCCTAAAGA AGGCTTATGA AATTCAGAAG AACAAACCAA GAAATGATGA TATTTTAAAG 720  
ATAATTATGG CAGCAATTGT GCTTTTCTTT TTCTTTTCCT GGATTCCCCA CCAAATATTC 780  
ACTTTTCTGG ATGTATTGAT TCAACTAGGC ATCATACGTG ACTGTAGAAT TGCAGATATT 840  
15 GTGGACACGG CCATGCCTAT CACCATTTGT ATAGCTTATT TTAACAATTG CCTGAATCCT 900  
CTTTTTTATG GCTTTCTGGG GAAAAAATTT AAAAGATATT TTCTCCAGCT TCTAAAATAT 960  
ATTCCCCCAA AAGCCAAATC CCACTCAAAC CTTTCAACAA AAATGAGCAC GCTTTCCTAC 1020  
CGCCCCCTCAG ATAATGTAAG CTCATCCACC AAGAAGCCTG CACCATGTTT TGAGGTTGAG 1080  
TGA 1083

20 (107) INFORMATION FOR SEQ ID NO:106:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 360 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

25 (D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:106:

Met Ile Leu Asn Ser Ser Thr Glu Asp Gly Ile Lys Arg Ile Gln Asp  
1 5 10 15

30 Asp Cys Pro Lys Ala Gly Arg His Asn Tyr Ile Phe Val Met Ile Pro

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	20	25	30
	Thr Leu Tyr Ser Ile Ile Phe Val Val Gly Ile Phe Gly Asn Ser Leu 35 40 45		
5	Val Val Ile Val Ile Tyr Phe Tyr Met Lys Leu Lys Thr Val Ala Ser 50 55 60		
	Val Phe Leu Leu Asn Leu Ala Leu Ala Asp Leu Cys Phe Leu Leu Thr 65 70 75 80		
	Leu Pro Leu Trp Ala Val Tyr Thr Ala Met Glu Tyr Arg Trp Pro Phe 85 90 95		
10	Gly Asn Tyr Leu Cys Lys Ile Ala Ser Ala Ser Val Ser Phe Asn Leu 100 105 110		
	Tyr Ala Ser Val Phe Leu Leu Thr Cys Leu Ser Ile Asp Arg Tyr Leu 115 120 125		
15	Ala Ile Val His Pro Met Lys Ser Arg Leu Arg Arg Thr Met Leu Val 130 135 140		
	Ala Lys Val Thr Cys Ile Ile Ile Trp Leu Leu Ala Gly Leu Ala Ser 145 150 155 160		
	Leu Pro Ala Ile Ile His Arg Asn Val Phe Phe Ile Glu Asn Thr Asn 165 170 175		
20	Ile Thr Val Cys Ala Phe His Tyr Glu Ser Gln Asn Ser Thr Leu Pro 180 185 190		
	Ile Gly Leu Gly Leu Thr Lys Asn Ile Leu Gly Phe Leu Phe Pro Phe 195 200 205		
25	Leu Ile Ile Leu Thr Ser Tyr Thr Leu Ile Trp Lys Ala Leu Lys Lys 210 215 220		
	Ala Tyr Glu Ile Gln Lys Asn Lys Pro Arg Asn Asp Asp Ile Phe Lys 225 230 235 240		
	Ile Ile Met Ala Ala Ile Val Leu Phe Phe Phe Phe Ser Trp Ile Pro 245 250 255		
30	His Gln Ile Phe Thr Phe Leu Asp Val Leu Ile Gln Leu Gly Ile Ile 260 265 270		
	Arg Asp Cys Arg Ile Ala Asp Ile Val Asp Thr Ala Met Pro Ile Thr 275 280 285		
35	Ile Cys Ile Ala Tyr Phe Asn Asn Cys Leu Asn Pro Leu Phe Tyr Gly 290 295 300		
	Phe Leu Gly Lys Lys Phe Lys Arg Tyr Phe Leu Gln Leu Leu Lys Tyr 305 310 315 320		



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Ile Pro Pro Lys Ala Lys Ser His Ser Asn Leu Ser Thr Lys Met Ser  
325 330 335

Thr Leu Ser Tyr Arg Pro Ser Asp Asn Val Ser Ser Ser Thr Lys Lys  
340 345 350

5 Pro Ala Pro Cys Phe Glu Val Glu  
355 360

(108) INFORMATION FOR SEQ ID NO:107:

- 10 (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 26 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA (genomic)
- (iv) ANTI-SENSE: NO

15 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:107:

CCCAAGCTTC CCCAGGTGTA TTTGAT

26

(109) INFORMATION FOR SEQ ID NO:108:

- 20 (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 38 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA (genomic)
- (iv) ANTI-SENSE: YES

25 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:108:

AAGCACAATT GCTGCATAAT TATCTTAAAA ATATCATC

38

(110) INFORMATION FOR SEQ ID NO:109:

- 30 (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 39 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA (genomic)
- (iv) ANTI-SENSE: NO

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:109:

AAGATAATTA TGGCAGCAAT TGTGCTTTC TTTTCTTT

39

(111) INFORMATION FOR SEQ ID NO:110:

(i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 26 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

10 (iv) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:110:

GTTGGATCCA CATAATGCAT TTTCTC

26

(112) INFORMATION FOR SEQ ID NO:111:

(i) SEQUENCE CHARACTERISTICS:

- 15 (A) LENGTH: 1344 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

20 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:111:

ATGGAGCTGC TAAAGCTGAA CCGGAGCGTG CAGGGAACCG GACCCGGGCC GGGGGCTTCC 60  
CTGTGCCGCC CGGGGGCGCC TCTCCTCAAC AGCAGCAGTG TGGGCAACCT CAGCTGCGAG 120  
CCCCCTCGCA TTCGCGGAGC CGGGACACGA GAATTGGAGC TGGCCATTAG AATCACTCTT 180  
TACGCAGTGA TCTTCCTGAT GAGCGTTGGA GGAAATATGC TCATCATCGT GGTCTTGGGA 240  
25 CTGAGCCGCC GCCTGAGGAC TGTCACCAAT GCCTTCCTCC TCTCACTGGC AGTCAGCGAC 300  
CTCCTGCTGG CTGTGGCTTG CATGCCCTTC ACCCTCCTGC CCAATCTCAT GGGCACATTC 360  
ATCTTTGGCA CCGTCATCTG CAAGGCGGTT TCCTACCTCA TGGGGGTGTC TGTGAGTGTG 420  
TCCACGCTAA GCCTCGTGGC CATCGCACTG GAGCGATATA GCGCCATCTG CCGACCACTG 480  
CAGGCACGAG TGTGGCAGAC GCGCTCCAC GCGGCTCGCG TGATTGTAGC CACGTGGCTG 540  
30 CTGTCCGGAC TACTCATGGT GCCCTACCCC GTGTACACTG TCGTGCAACC AGTGGGGCCT 600  
CGTGTGCTGC AGTGCGTGCA TCGCTGGCCC AGTGCGCGGG TCCGCCAGAC CTGGTCCGTA 660

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CTGCTGCTTC TGCTCTTGTT CTTTCATCCCA GGTGTGGTTA TGGCCGTGGC CTACGGGCTT 720  
 ATCTCTCGCG AGCTCTACTT AGGGCTTCGC TTTGACGGCG ACAGTGACAG CGACAGCCAA 780  
 AGCAGGGTCC GAAACCAAGG CGGGCTGCCA GGGGCTGTTC ACCAGAACGG GCGTTGCCGG 840  
 CCTGAGACTG GCGCGGTTGG CAAAGACAGC GATGGCTGCT ACGTGCAACT TCCACGTTCC 900  
 5 CGGCCTGCCC TGGAGCTGAC GGCCTGACG GCTCCTGGGC CGGGATCCGG CTCCCGGCCC 960  
 ACCCAGGCCA AGCTGCTGGC TAAGAAGCGC GTGAAACGAA TGTGCTGGT GATCGTTGTG 1020  
 CTTTTTTTTC TGTGTTGGTT GCCAGTTTAT AGTGCCAACA CGTGGCGCGC CTTTGATGGC 1080  
 CCGGGTGAC ACCGAGCACT CTCGGGTGCT CCTATCTCCT TCATTCACTT GCTGAGCTAC 1140  
 GCCTCGGCCCT GTGTCAACCC CCTGGTCTAC TGCTTCATGC ACCGTCGCTT TCGCCAGGCC 1200  
 10 TGCTTGAAA CTGCGCTCG CTGCTGCCCC CGGCCTCCAC GAGCTCGCCC CAGGGCTCTT 1260  
 CCCGATGAGG ACCCTCCCAC TCCCTCCATT GCTTCGCTGT CCAGGCTTAG CTACACCACC 1320  
 ATCAGCACAC TGGGCCCTGG CTGA 1344

(113) INFORMATION FOR SEQ ID NO:112:

- (i) SEQUENCE CHARACTERISTICS:  
 15 (A) LENGTH: 447 amino acids  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS:  
 (D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein

20 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:112:

Met Glu Leu Leu Lys Leu Asn Arg Ser Val Gln Gly Thr Gly Pro Gly  
 1 5 10 15  
 Pro Gly Ala Ser Leu Cys Arg Pro Gly Ala Pro Leu Leu Asn Ser Ser  
 20 25 30  
 25 Ser Val Gly Asn Leu Ser Cys Glu Pro Pro Arg Ile Arg Gly Ala Gly  
 35 40 45  
 Thr Arg Glu Leu Glu Leu Ala Ile Arg Ile Thr Leu Tyr Ala Val Ile  
 50 55 60  
 30 Phe Leu Met Ser Val Gly Gly Asn Met Leu Ile Ile Val Val Leu Gly  
 65 70 75 80  
 Leu Ser Arg Arg Leu Arg Thr Val Thr Asn Ala Phe Leu Leu Ser Leu  
 85 90 95

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Ala Val Ser Asp Leu Leu Leu Ala Val Ala Cys Met Pro Phe Thr Leu  
100 105 110

Leu Pro Asn Leu Met Gly Thr Phe Ile Phe Gly Thr Val Ile Cys Lys  
115 120 125

5 Ala Val Ser Tyr Leu Met Gly Val Ser Val Ser Val Ser Thr Leu Ser  
130 135 140

Leu Val Ala Ile Ala Leu Glu Arg Tyr Ser Ala Ile Cys Arg Pro Leu  
145 150 155 160

10 Gln Ala Arg Val Trp Gln Thr Arg Ser His Ala Ala Arg Val Ile Val  
165 170 175

Ala Thr Trp Leu Leu Ser Gly Leu Leu Met Val Pro Tyr Pro Val Tyr  
180 185 190

Thr Val Val Gln Pro Val Gly Pro Arg Val Leu Gln Cys Val His Arg  
195 200 205

15 Trp Pro Ser Ala Arg Val Arg Gln Thr Trp Ser Val Leu Leu Leu Leu  
210 215 220

Leu Leu Phe Phe Ile Pro Gly Val Val Met Ala Val Ala Tyr Gly Leu  
225 230 235 240

20 Ile Ser Arg Glu Leu Tyr Leu Gly Leu Arg Phe Asp Gly Asp Ser Asp  
245 250 255

Ser Asp Ser Gln Ser Arg Val Arg Asn Gln Gly Gly Leu Pro Gly Ala  
260 265 270

Val His Gln Asn Gly Arg Cys Arg Pro Glu Thr Gly Ala Val Gly Lys  
275 280 285

25 Asp Ser Asp Gly Cys Tyr Val Gln Leu Pro Arg Ser Arg Pro Ala Leu  
290 295 300

Glu Leu Thr Ala Leu Thr Ala Pro Gly Pro Gly Ser Gly Ser Arg Pro  
305 310 315 320

30 Thr Gln Ala Lys Leu Leu Ala Lys Lys Arg Val Lys Arg Met Leu Leu  
325 330 335

Val Ile Val Val Leu Phe Phe Leu Cys Trp Leu Pro Val Tyr Ser Ala  
340 345 350

Asn Thr Trp Arg Ala Phe Asp Gly Pro Gly Ala His Arg Ala Leu Ser  
355 360 365

35 Val Ala Pro Ile Ser Phe Ile His Leu Leu Ser Tyr Ala Ser Ala Cys  
370 375 380

Val Asn Pro Leu Val Tyr Cys Phe Met His Arg Arg Phe Arg Gln Ala

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385                                      390                                      395                                      400

Cys Leu Glu Thr Cys Ala Arg Cys Cys Pro Arg Pro Pro Arg Ala Arg  
    405                                      410                                      415

5                                      420                                      425                                      430

Pro Arg Ala Leu Pro Asp Glu Asp Pro Pro Thr Pro Ser Ile Ala Ser

Leu Ser Arg Leu Ser Tyr Thr Thr Ile Ser Thr Leu Gly Pro Gly  
    435                                      440                                      445

(114) INFORMATION FOR SEQ ID NO:113:

- 10                                      (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 34 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA (genomic)

15                                      (xi) SEQUENCE DESCRIPTION: SEQ ID NO:113:

CAGCAGCATG CGCTTCACGC GCTTCTTAGC CCAG

34

(115) INFORMATION FOR SEQ ID NO:114:

- 20                                      (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 33 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: not relevant
- (ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:114:

25 AGAAGCGCGT GAAGCGCATG CTGCTGGTGA TCGTT

35

(116) INFORMATION FOR SEQ ID NO:115:

- 30                                      (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 33 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA (genomic)

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:115:

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ATGGAGAAAA GAATCAAAAG AATGTTCTAT ATA

33

(117) INFORMATION FOR SEQ ID NO:116:

(i) SEQUENCE CHARACTERISTICS:

5

- (A) LENGTH: 33 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iv) ANTI-SENSE: YES

10

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:116:

TATATAGAAC ATTCTTTGA TTCTTTCTC CAT

33

(118) INFORMATION FOR SEQ ID NO:117:

(i) SEQUENCE CHARACTERISTICS:

15

- (A) LENGTH: 30 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iv) ANTI-SENSE: NO

20

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:117:

CGCTCTCTGG CCTTGAAGCG CACGCTCAGC

30

(119) INFORMATION FOR SEQ ID NO:118:

(i) SEQUENCE CHARACTERISTICS:

25

- (A) LENGTH: 30 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iv) ANTI-SENSE: YES

30

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:118:

GCTGAGCGTG CGCTTCAAGG CCAGAGAGCG

30

(120) INFORMATION FOR SEQ ID NO:119:

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(i) SEQUENCE CHARACTERISTICS:  
    (A) LENGTH: 30 base pairs  
    (B) TYPE: nucleic acid  
    (C) STRANDEDNESS: single  
5     (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:119:

CCCAGGAAAA AGGTGAAAGT CAAAGTTTTC

30

10 (121) INFORMATION FOR SEQ ID NO:120:

(i) SEQUENCE CHARACTERISTICS:  
    (A) LENGTH: 30 base pairs  
    (B) TYPE: nucleic acid  
    (C) STRANDEDNESS: single  
15     (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iv) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:120:

GAAAACTTTG ACTTTCACCT TTTTCCTGGG

30

20 (122) INFORMATION FOR SEQ ID NO:121:

(i) SEQUENCE CHARACTERISTICS:  
    (A) LENGTH: 27 base pairs  
    (B) TYPE: nucleic acid  
    (C) STRANDEDNESS: single  
25     (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:121:

GGGGCGCGGG TGAAACGGCT GGTGAGC

27

30 (123) INFORMATION FOR SEQ ID NO:122:

(i) SEQUENCE CHARACTERISTICS:  
    (A) LENGTH: 27 base pairs  
    (B) TYPE: nucleic acid  
    (C) STRANDEDNESS: single

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(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iv) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:122:

5 GCTCACCAGC CGTTTCACCC GCGCCCC

27

(124) INFORMATION FOR SEQ ID NO:123:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 30 base pairs

(B) TYPE: nucleic acid

10 (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:123:

15 CCCCTTGAAA AGCCTAAGAA CTTGGTCATC

30

(125) INFORMATION FOR SEQ ID NO:124:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 30 base pairs

(B) TYPE: nucleic acid

20 (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iv) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:124:

25 GATGACCAAG TTCTTAGGCT TTTCAAGGGG

30

(126) INFORMATION FOR SEQ ID NO:125:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 32 base pairs

(B) TYPE: nucleic acid

30 (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)



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(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:125:

GATCTCTAGA ATGAACAGCA CATGTATTGA AG

32

(127) INFORMATION FOR SEQ ID NO:126:

- 5 (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 35 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

10 (ii) MOLECULE TYPE: DNA (genomic)

(iv) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:126:

CTAGGGTACC CGCTCAAGGA CCTCTAATTC CATAG

35

(128) INFORMATION FOR SEQ ID NO:127:

- 15 (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 1296 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

20 (ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:127:

ATGCAGGCGC TTAACATTAC CCCGGAGCAG TTCTCTCGGC TGCTGCGGGA CCACAACCTG 60  
ACGCGGGAGC AGTTCATCGC TCTGTACCGG CTGCGACCGC TCGTCTACAC CCCAGAGCTG 120  
CCGGGACGCG CCAAGCTGGC CCTCGTGCTC ACCGGCGTGC TCATCTTCGC CCTGGCGCTC 180  
25 TTTGGCAATG CTCTGGTGTT CTACGTGGTG ACCCGCAGCA AGGCCATGCG CACCGTCACC 240  
AACATCTTTA TCTGCTCCTT GCGCTCAGT GACCTGCTCA TCACCTTCTT CTGCATTCCC 300  
GTCACCATGC TCCAGAACAT TTCCGACAAC TGGCTGGGGG GTGCTTTCAT TTGCAAGATG 360  
GTGCCATTTG TCCAGTCTAC CGCTGTTGTG ACAGAAATGC TCACTATGAC CTGCATTGCT 420  
GTGGAAAGGC ACCAGGGACT TGTGCATCCT TTTAAATGA AGTGGCAATA CACCAACCGA 480

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AGGGCTTTCA CAATGCTAGG TGTGGTCTGG CTGGTGGCAG TCATCGTAGG ATCACCCATG 540  
 TGGCACGTGC AACAACTTGA GATCAAATAT GACTTCCTAT ATGAAAAGGA ACACATCTGC 600  
 TGCTTAGAAG AGTGGACCAG CCCTGTGCAC CAGAAGATCT ACACCACCTT CATCCTTGTC 660  
 ATCCTCTTCC TCCTGCCTCT TATGGTGATG CTTATTCTGT ACAGTAAAAT TGGTTATGAA 720  
 5 CTTTGGATAA AGAAAAGAGT TGGGGATGGT TCAGTGCTTC GAACTATTCA TGGAAAAGAA 780  
 ATGTCCAAAA TAGCCAGGAA GAAGAAACGA GCTAAGATTA TGATGGTGAC AGTGGTGGCT 840  
 CTCTTTGCTG TGTGCTGGGC ACCATTCCAT GTTGTCCATA TGATGATTGA ATACAGTAAT 900  
 TTTGAAAAGG AATATGATGA TGTCACAATC AAGATGATTT TTGCTATCGT GCAAATTATT 960  
 GGATTTTCCA ACTCCATCTG TAATCCCATT GTCTATGCAT TTATGAATGA AAACTTCAAA 1020  
 10 AAAAAATGTTT TGTCTGCAGT TTGTTATTGC ATAGTAAATA AAACCTTCTC TCCAGCACAA 1080  
 AGGCATGGAA ATTCAGGAAT TACAATGATG CGGAAGAAAG CAAAGTTTTC CCTCAGAGAG 1140  
 AATCCAGTGG AGGAAACCAA AGGAGAAGCA TTCAGTGATG GCAACATTGA AGTCAAATTG 1200  
 TGTGAACAGA CAGAGGAGAA GAAAAAGCTC AAACGACATC TTGCTCTCTT TAGGTCTGAA 1260  
 CTGGCTGAGA ATTCTCCTTT AGACAGTGGG CATTAA 1296

15 (129) INFORMATION FOR SEQ ID NO:128:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 431 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

20 (D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:128:

Met Gln Ala Leu Asn Ile Thr Pro Glu Gln Phe Ser Arg Leu Leu Arg  
 1 5 10 15  
 25 Asp His Asn Leu Thr Arg Glu Gln Phe Ile Ala Leu Tyr Arg Leu Arg  
 20 25 30  
 Pro Leu Val Tyr Thr Pro Glu Leu Pro Gly Arg Ala Lys Leu Ala Leu  
 35 40 45  
 30 Val Leu Thr Gly Val Leu Ile Phe Ala Leu Ala Leu Phe Gly Asn Ala  
 50 55 60  
 Leu Val Phe Tyr Val Val Thr Arg Ser Lys Ala Met Arg Thr Val Thr  
 65 70 75 80

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	Asn Ile Phe Ile Cys Ser Leu Ala Leu Ser Asp Leu Leu Ile Thr Phe	85	90	95
	Phe Cys Ile Pro Val Thr Met Leu Gln Asn Ile Ser Asp Asn Trp Leu	100	105	110
5	Gly Gly Ala Phe Ile Cys Lys Met Val Pro Phe Val Gln Ser Thr Ala	115	120	125
	Val Val Thr Glu Met Leu Thr Met Thr Cys Ile Ala Val Glu Arg His	130	135	140
10	Gln Gly Leu Val His Pro Phe Lys Met Lys Trp Gln Tyr Thr Asn Arg	145	150	155
	Arg Ala Phe Thr Met Leu Gly Val Val Trp Leu Val Ala Val Ile Val	165	170	175
	Gly Ser Pro Met Trp His Val Gln Gln Leu Glu Ile Lys Tyr Asp Phe	180	185	190
15	Leu Tyr Glu Lys Glu His Ile Cys Cys Leu Glu Glu Trp Thr Ser Pro	195	200	205
	Val His Gln Lys Ile Tyr Thr Thr Phe Ile Leu Val Ile Leu Phe Leu	210	215	220
20	Leu Pro Leu Met Val Met Leu Ile Leu Tyr Ser Lys Ile Gly Tyr Glu	225	230	235
	Leu Trp Ile Lys Lys Arg Val Gly Asp Gly Ser Val Leu Arg Thr Ile	245	250	255
	His Gly Lys Glu Met Ser Lys Ile Ala Arg Lys Lys Lys Arg Ala Lys	260	265	270
25	Ile Met Met Val Thr Val Val Ala Leu Phe Ala Val Cys Trp Ala Pro	275	280	285
	Phe His Val Val His Met Met Ile Glu Tyr Ser Asn Phe Glu Lys Glu	290	295	300
30	Tyr Asp Asp Val Thr Ile Lys Met Ile Phe Ala Ile Val Gln Ile Ile	305	310	315
	Gly Phe Ser Asn Ser Ile Cys Asn Pro Ile Val Tyr Ala Phe Met Asn	325	330	335
	Glu Asn Phe Lys Lys Asn Val Leu Ser Ala Val Cys Tyr Cys Ile Val	340	345	350
35	Asn Lys Thr Phe Ser Pro Ala Gln Arg His Gly Asn Ser Gly Ile Thr	355	360	365
	Met Met Arg Lys Lys Ala Lys Phe Ser Leu Arg Glu Asn Pro Val Glu			

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370 375 380

Glu Thr Lys Gly Glu Ala Phe Ser Asp Gly Asn Ile Glu Val Lys Leu  
 385 390 395 400

5 Cys Glu Gln Thr Glu Glu Lys Lys Lys Leu Lys Arg His Leu Ala Leu  
 405 410 415

Phe Arg Ser Glu Leu Ala Glu Asn Ser Pro Leu Asp Ser Gly His  
 420 425 430

(130) INFORMATION FOR SEQ ID NO:129:

- (i) SEQUENCE CHARACTERISTICS:
- 10 (A) LENGTH: 2040 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

- 15 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:129:

ATGGGCAGCC CCTGGAACGG CAGCGACGGC CCCGAGGGGG CGCGGGAGCC GCCGTGGCCC  
 60

GCGCTGCCGC CTTGCGACGA GCGCCGCTGC TCGCCCTTTC CCCTGGGGGC GCTGGTGCCG  
 120

20 GTGACCGCTG TGTGCCTGTG CCTGTTCGTC GTCGGGGTGA GCGGCAACGT GGTGACCGTG  
 180

ATGCTGATCG GCGCTACCG GGACATGCGG ACCACCACCA ACTTGACCT GGGCAGCATG  
 240

25 GCCGTGTCCG ACCTACTCAT CCTGCTCGGG CTGCCGTTTC ACCTGTACCG CCTCTGGCGC  
 300

TCGCGGCCCT GGGTGTTCGG GCCGCTGCTC TGCCGCCTGT CCCTCTACGT GGGCGAGGGC  
 360

TGCACCTACG CCACGCTGCT GCACATGACC GCGCTCAGCG TCGAGCGCTA CCTGGCCATC  
 30 420

TGCCGCCCCG TCCGCGCCCG CGTCTTGGTC ACCCGGCGCC GCGTCCGCGC GTCATCGCT  
 480

35 GTGCTCTGGG CCGTGGCGCT GCTCTCTGCC GGTCCCTTCT TGTTCCTGGT GGGCGTCGAG  
 540

CAGGACCCCG GCATCTCCGT AGTCCCGGGC CTCAATGGCA CCGCGCGGAT CGCCTCCTCG  
 600

40 CCTCTCGCCT CGTCGCCGCC TCTCTGGCTC TCGCGGGCGC CACCGCCGTC CCCGCCGTCG

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660  
GGGCCCCGAGA CCGCGGAGGC CGCGGCGCTG TTCAGCCGCG AATGCCGGCC GAGCCCCGCG  
720  
5 CAGCTGGGCG CGCTGCGTGT CATGCTGTGG GTCACCACCG CCTACTTCTT CCTGCCCTTT  
780  
CTGTGCCTCA GCATCCTCTA CGGGCTCATC GGGCGGGAGC TGTGGAGCAG CCGGCGGCCG  
10 840  
CTGCGAGGCC CGGCCGCCTC GGGGCGGGAG AGAGGCCACC GGCAGACCAA ACGCGTCCTG  
900  
15 CGTAAGTGA GCGCCCGTGG TTCAAAGAC GCCTGCCTGC AGTCCGCCCC GCGGGGAGC  
960  
GCGCAAACGC TGGGTCCCCT TCCCCTGCTC GCCCAGCTCT GGGCGCCGCT TCCAGTCCC  
1020  
20 TTCTCTATTT CGATTCCAGC CTCCACCCGC CGTACTTCC CATCCCCGA GAAAACCATG  
1080  
TCCTGTCCCC CAGGAGCTCT GGGGACCCC AGGGCGCTTT GAGGGTGGGA TCCCCGATC  
25 1140  
CGATTGAGTA ACCAGCAGTG CTTTCCAGA GCCTCTGAGA CCAGAAAGGA GAGTTGGTAA  
1200  
30 TTCTTAATCC AACCACCTGT TAGATGCCAC AAATGAGGAG TCCTCACAGT GCTCTTGAGA  
1260  
AGACGAGGGA GATTTCATTA AGCTAAAATT TTTATTTAA TGTTAAGTGA TGCTGAAGGC  
1320  
35 TAAAGTAAAC CTTGCTCGTA TCAAAAAGTA AAGATTGTGC AGACCTGTTG TAGAATTCTT  
1380  
TTCAACAGAG AACAGAAAAC TTGTCTCCGA AGTGGGTTTG TGGAAGGAAG CCTGCCAAGG  
40 1440  
CGGCTTGTTT AGAGAAATTG CTCCTTCTGG TTTATGTCCA GCCTTGATAA CACATATGGG  
1500  
45 AGCCTACTAT GCAGTTTTAA AGCAAGTATC CATGCAGCCT GCAGCCTGGT CATTTTTTCT  
1560  
GGGGTGAGGA TCTGCCTAGG TAGAAGTTTT CTCTAATTTA TTTTGCTGTT ACTTGTTATT  
1620  
50 GCAGATGGTT CCTTGTCGGG GTGGGGGGTT TATTTGCTTC CCAATGCTTT TGTTAATCCC  
1680  
GGTGCTGTGT CTTATGTTGC AGTGGTGGTG GTTCTGGCAT TTATAATTTG CTGGTTGCCC  
55 1740

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TTCCACGTTG GCAGAATCAT TTACATAAAC ACGGAAGATT CGCGGATGAT GTACTTCTCT  
1800

5 CAGTACTTTA ACATCGTCGC TCTGCAACTT TTCTATCTGA GCGCATCTAT CAACCCAATC  
1860

CTCTACAACC TCATTTCAAA GAAGTACAGA GCGGCGGCCT TTAAACTGCT GCTCGCAAGG  
1920

10 AAGTCCAGGC CGAGAGGCTT CCACAGAAGC AGGGACACTG CGGGGGAAGT TGCAGGGGAC  
1980

15 ACTGGAGGAG ACACGGTGGG CTACACCGAG ACAAGCGCTA ACGTGAAGAC GATGGGATAA  
2040

(131) INFORMATION FOR SEQ ID NO:130:

(i) SEQUENCE CHARACTERISTICS:

- 20 (A) LENGTH: 412 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:130:

25 Met Gly Ser Pro Trp Asn Gly Ser Asp Gly Pro Glu Gly Ala Arg Glu  
1 5 10 15  
Pro Pro Trp Pro Ala Leu Pro Pro Cys Asp Glu Arg Arg Cys Ser Pro  
20 25 30  
Phe Pro Leu Gly Ala Leu Val Pro Val Thr Ala Val Cys Leu Cys Leu  
35 40 45  
30 Phe Val Val Gly Val Ser Gly Asn Val Val Thr Val Met Leu Ile Gly  
50 55 60  
Arg Tyr Arg Asp Met Arg Thr Thr Thr Asn Leu Tyr Leu Gly Ser Met  
65 70 75 80  
35 Ala Val Ser Asp Leu Leu Ile Leu Leu Gly Leu Pro Phe Asp Leu Tyr  
85 90 95  
Arg Leu Trp Arg Ser Arg Pro Trp Val Phe Gly Pro Leu Leu Cys Arg  
100 105 110  
Leu Ser Leu Tyr Val Gly Glu Gly Cys Thr Tyr Ala Thr Leu Leu His  
115 120 125  
40 Met Thr Ala Leu Ser Val Glu Arg Tyr Leu Ala Ile Cys Arg Pro Leu  
130 135 140

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Arg Ala Arg Val Leu Val Thr Arg Arg Arg Val Arg Ala Leu Ile Ala  
 145 150 155 160  
 Val Leu Trp Ala Val Ala Leu Leu Ser Ala Gly Pro Phe Leu Phe Leu  
 165 170 175  
 5 Val Gly Val Glu Gln Asp Pro Gly Ile Ser Val Val Pro Gly Leu Asn  
 180 185 190  
 Gly Thr Ala Arg Ile Ala Ser Ser Pro Leu Ala Ser Ser Pro Pro Leu  
 195 200 205  
 10 Trp Leu Ser Arg Ala Pro Pro Pro Ser Pro Pro Ser Gly Pro Glu Thr  
 210 215 220  
 Ala Glu Ala Ala Ala Leu Phe Ser Arg Glu Cys Arg Pro Ser Pro Ala  
 225 230 235 240  
 Gln Leu Gly Ala Leu Arg Val Met Leu Trp Val Thr Thr Ala Tyr Phe  
 245 250 255  
 15 Phe Leu Pro Phe Leu Cys Leu Ser Ile Leu Tyr Gly Leu Ile Gly Arg  
 260 265 270  
 Glu Leu Trp Ser Ser Arg Arg Pro Leu Arg Gly Pro Ala Ala Ser Gly  
 275 280 285  
 20 Arg Glu Arg Gly His Arg Gln Thr Lys Arg Val Leu Leu Val Val Val  
 290 295 300  
 Leu Ala Phe Ile Ile Cys Trp Leu Pro Phe His Val Gly Arg Ile Ile  
 305 310 315 320  
 Tyr Ile Asn Thr Glu Asp Ser Arg Met Met Tyr Phe Ser Gln Tyr Phe  
 325 330 335  
 25 Asn Ile Val Ala Leu Gln Leu Phe Tyr Leu Ser Ala Ser Ile Asn Pro  
 340 345 350  
 Ile Leu Tyr Asn Leu Ile Ser Lys Lys Tyr Arg Ala Ala Ala Phe Lys  
 355 360 365  
 30 Leu Leu Leu Ala Arg Lys Ser Arg Pro Arg Gly Phe His Arg Ser Arg  
 370 375 380  
 Asp Thr Ala Gly Glu Val Ala Gly Asp Thr Gly Gly Asp Thr Val Gly  
 385 390 395 400  
 Tyr Thr Glu Thr Ser Ala Asn Val Lys Thr Met Gly  
 405 410

35 (132) INFORMATION FOR SEQ ID NO:131:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 1344 base pairs

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- (B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

5 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:131:

ATGGAGCTGC TAAAGCTGAA CCGGAGCGTG CAGGGAACCG GACCCGGGCC GGGGGCTTCC  
60  
CTGTGCCGCC CGGGGGCGCC TCTCCTCAAC AGCAGCAGTG TGGGCAACCT CAGCTGCGAG  
120  
10 CCCCCTCGCA TTCGCGGAGC CGGGACACGA GAATTGGAGC TGGCCATTAG AATCACTCTT  
180  
TACGCAGTGA TCTTCTGAT GAGCGTTGGA GGAAATATGC TCATCATCGT GGTCTTGGGA  
240  
CTGAGCCGCC GCCTGAGGAC TGTACCAAT GCCTTCCTCC TCTACTGGC AGTCAGCGAC  
15 300  
CTCCTGCTGG CTGTGGCTTG CATGCCCTTC ACCCTCCTGC CCAATCTCAT GGGCACATTC  
360  
ATCTTTGGCA CCGTCATCTG CAAGGCGGTT TCCTACCTCA TGGGGGTGTC TGTGAGTGTG  
420  
20 TCCACGCTAA GCCTCGTGGC CATCGCACTG GAGCGATATA GCGCCATCTG CCGACCACTG  
480  
CAGGCACGAG TGTGGCAGAC GCGCTCCAC GCGGCTCGCG TGATTGTAGC CACGTGGCTG  
540  
CTGTCCGGAC TACTCATGGT GCCCTACCCC GTGTACACTG TCGTGCAACC AGTGGGGCCT  
25 600  
CGTGTGCTGC AGTGCGTGCA TCGCTGGCCC AGTGCGCGGG TCCGCCAGAC CTGGTCCGTA  
660  
CTGCTGCTTC TGCTCTGTT CTTATCCCA GGTGTGGTTA TGGCCGTGGC CTACGGGCTT  
720  
30 ATCTCTCGCG AGCTCTACTT AGGGCTTCGC TTTGACGGCG ACAGTGACAG CGACAGCCAA  
780  
AGCAGGGTCC GAAACCAAGG CGGGCTGCCA GGGGCTGTTC ACCAGAACGG GCGTTGCCGG  
840  
CCTGAGACTG GCGCGGTTGG CAAAGACAGC GATGGCTGCT ACGTGCAACT TCCACGTTCC  
35 900  
CGGCCTGCCC TGGAGCTGAC GGCCTGACG GCTCCTGGGC CGGGATCCGG CTCCCGGCCC



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960

ACCCAGGCCA AGCTGCTGGC TAAGAAGCGC GTGAAACGAA TGTGCTGGT GATCGTTGTG  
1020

CTTTTTC TGTGTTGGTT GCCAGTTTAT AGTGCCAACA CGTGGCGCGC CTTTGATGGC  
5 1080

CCGGGTGCAC ACCGAGCACT CTCGGGTGCT CCTATCTCCT TCATTCACCT GCTGAGCTAC  
1140

GCCTCGGCCT GTGTCAACCC CCTGGTCTAC TGCTTCATGC ACCGTCGCTT TCGCCAGGCC  
1200

10 TGCCTGGAAC CTTGCGCTCG CTGCTGCCCC CGGCCTCCAC GAGCTCGCCC CAGGGCTCTT  
1260

CCCGATGAGG ACCCTCCAC TCCCTCCATT GCTTCGCTGT CCAGGCTTAG CTACACCACC  
1320

ATCAGCACAC TGGGCCCTGG CTGA  
15 1344

(133) INFORMATION FOR SEQ ID NO:132:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 447 amino acids  
(B) TYPE: amino acid  
20 (C) STRANDEDNESS:  
(D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:132:

25 Met Glu Leu Leu Lys Leu Asn Arg Ser Val Gln Gly Thr Gly Pro Gly  
1 5 10 15  
Pro Gly Ala Ser Leu Cys Arg Pro Gly Ala Pro Leu Leu Asn Ser Ser  
20 25 30  
Ser Val Gly Asn Leu Ser Cys Glu Pro Pro Arg Ile Arg Gly Ala Gly  
35 40 45  
30 Thr Arg Glu Leu Glu Leu Ala Ile Arg Ile Thr Leu Tyr Ala Val Ile  
50 55 60  
Phe Leu Met Ser Val Gly Gly Asn Met Leu Ile Ile Val Val Leu Gly  
65 70 75 80  
35 Leu Ser Arg Arg Leu Arg Thr Val Thr Asn Ala Phe Leu Leu Ser Leu  
85 90 95  
Ala Val Ser Asp Leu Leu Leu Ala Val Ala Cys Met Pro Phe Thr Leu

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	100	105	110
	Leu Pro Asn Leu Met Gly Thr Phe Ile Phe Gly Thr Val Ile Cys Lys 115 120 125		
5	Ala Val Ser Tyr Leu Met Gly Val Ser Val Ser Val Ser Thr Leu Ser 130 135 140		
	Leu Val Ala Ile Ala Leu Glu Arg Tyr Ser Ala Ile Cys Arg Pro Leu 145 150 155 160		
	Gln Ala Arg Val Trp Gln Thr Arg Ser His Ala Ala Arg Val Ile Val 165 170 175		
10	Ala Thr Trp Leu Leu Ser Gly Leu Leu Met Val Pro Tyr Pro Val Tyr 180 185 190		
	Thr Val Val Gln Pro Val Gly Pro Arg Val Leu Gln Cys Val His Arg 195 200 205		
15	Trp Pro Ser Ala Arg Val Arg Gln Thr Trp Ser Val Leu Leu Leu Leu 210 215 220		
	Leu Leu Phe Phe Ile Pro Gly Val Val Met Ala Val Ala Tyr Gly Leu 225 230 235 240		
	Ile Ser Arg Glu Leu Tyr Leu Gly Leu Arg Phe Asp Gly Asp Ser Asp 245 250 255		
20	Ser Asp Ser Gln Ser Arg Val Arg Asn Gln Gly Gly Leu Pro Gly Ala 260 265 270		
	Val His Gln Asn Gly Arg Cys Arg Pro Glu Thr Gly Ala Val Gly Lys 275 280 285		
25	Asp Ser Asp Gly Cys Tyr Val Gln Leu Pro Arg Ser Arg Pro Ala Leu 290 295 300		
	Glu Leu Thr Ala Leu Thr Ala Pro Gly Pro Gly Ser Gly Ser Arg Pro 305 310 315 320		
	Thr Gln Ala Lys Leu Leu Ala Lys Lys Arg Val Lys Arg Met Leu Leu 325 330 335		
30	Val Ile Val Val Leu Phe Phe Leu Cys Trp Leu Pro Val Tyr Ser Ala 340 345 350		
	Asn Thr Trp Arg Ala Phe Asp Gly Pro Gly Ala His Arg Ala Leu Ser 355 360 365		
35	Val Ala Pro Ile Ser Phe Ile His Leu Leu Ser Tyr Ala Ser Ala Cys 370 375 380		
	Val Asn Pro Leu Val Tyr Cys Phe Met His Arg Arg Phe Arg Gln Ala 385 390 395 400		

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Cys Leu Glu Thr Cys Ala Arg Cys Cys Pro Arg Pro Pro Arg Ala Arg  
 405 410 415

Pro Arg Ala Leu Pro Asp Glu Asp Pro Pro Thr Pro Ser Ile Ala Ser  
 420 425 430

5 Leu Ser Arg Leu Ser Tyr Thr Thr Ile Ser Thr Leu Gly Pro Gly  
 435 440 445

(134) INFORMATION FOR SEQ ID NO:133:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1014 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:133:

15 ATGAACAGCA CATGTATTGA AGAACAGCAT GACCTGGATC ACTATTTGTT TCCCATTTGTT 60  
 TACATCTTTG TGATTATAGT CAGCATTCCA GCCAATATTG GATCTCTGTG TGTGTCTTTC 120  
 CTGCAAGCAA AGAAGGAAAG TGAAC TAGGA ATTTACCTCT TCAGTTTGTG ACTATCAGAT 180  
 TTACTCTATG CATTAACTCT CCCTTTATGG ATTGATTATA CTTGGAATAA AGACAACTGG 240  
 ACTTTCTCTC CTGCCTTGTG CAAAGGGAGT GCTTTTCTCA TGTACATGAA TTTTACAGC 300  
 20 AGCACAGCAT TCCTCACCTG CATTGCCGTT GATCGGTATT TGGCTGTTGT CTACCCTTTG 360  
 AAGTTTTTTT TCCTAAGGAC AAGAAGATT GCACATCATG TCAGCCTGTC CATCTGGATA 420  
 TTGGAACCA TCTTCAATGC TGTCATGTTG TGGGAAGATG AAACAGTTGT TGAATATTGC 480  
 GATGCCGAAA AGTCTAATT TACTTTATGC TATGACAAAT ACCCTTTAGA GAAATGGCAA 540  
 ATCAACCTCA ACTTGTTTCTG GACGTGTACA GGCTATGCAA TACCTTTGGT CACCATCCTG 600  
 25 ATCTGTAACC GGAAAGTCTA CCAAGCTGTG CGGCACAATA AAGCCACGGA AAACAAGGAA 660  
 AAGAAGAGAA TCAAAAACT ACTTGTCAGC ATCACAGTTA CTTTGTCTT ATGCTTTACT 720  
 CCCTTTCATG TGATGTTGCT GATTCGCTGC ATTTTAGAGC ATGCTGTGAA CTTGAAGAC 780  
 CACAGCAATT CTGGGAAGCG AACTTACACA ATGTATAGAA TCACGGTTGC ATTAACAAGT 840  
 TTAAATTGTG TTGCTGATCC AATTCTGTAC TGTTTTGTTA CCGAAACAGG AAGATATGAT 900  
 30 ATGTGGAATA TATTAAATTT CTGCACTGGG AGGTGTAATA CATCACAAG ACAAGAAAA 960  
 CGCATACTTT CTGTGTCTAC AAAAGATACT ATGGAATTAG AGGTCCTTGA GTAG 1014

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(135) INFORMATION FOR SEQ ID NO:134:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 337 amino acids  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS:  
 (D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:134:

Met Asn Ser Thr Cys Ile Glu Glu Gln His Asp Leu Asp His Tyr Leu  
 1 5 10 15

Phe Pro Ile Val Tyr Ile Phe Val Ile Ile Val Ser Ile Pro Ala Asn  
 20 25 30

Ile Gly Ser Leu Cys Val Ser Phe Leu Gln Ala Lys Lys Glu Ser Glu  
 35 40 45

Leu Gly Ile Tyr Leu Phe Ser Leu Ser Leu Ser Asp Leu Leu Tyr Ala  
 50 55 60

Leu Thr Leu Pro Leu Trp Ile Asp Tyr Thr Trp Asn Lys Asp Asn Trp  
 65 70 75 80

Thr Phe Ser Pro Ala Leu Cys Lys Gly Ser Ala Phe Leu Met Tyr Met  
 85 90 95

Asn Phe Tyr Ser Ser Thr Ala Phe Leu Thr Cys Ile Ala Val Asp Arg  
 100 105 110

Tyr Leu Ala Val Val Tyr Pro Leu Lys Phe Phe Phe Leu Arg Thr Arg  
 115 120 125

Arg Phe Ala Leu Met Val Ser Leu Ser Ile Trp Ile Leu Glu Thr Ile  
 130 135 140

Phe Asn Ala Val Met Leu Trp Glu Asp Glu Thr Val Val Glu Tyr Cys  
 145 150 155 160

Asp Ala Glu Lys Ser Asn Phe Thr Leu Cys Tyr Asp Lys Tyr Pro Leu  
 165 170 175

Glu Lys Trp Gln Ile Asn Leu Asn Leu Phe Arg Thr Cys Thr Gly Tyr  
 180 185 190

Ala Ile Pro Leu Val Thr Ile Leu Ile Cys Asn Arg Lys Val Tyr Gln  
 195 200 205

Ala Val Arg His Asn Lys Ala Thr Glu Asn Lys Glu Lys Lys Arg Ile  
 210 215 220

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Lys Lys Leu Leu Val Ser Ile Thr Val Thr Phe Val Leu Cys Phe Thr  
 225 230 235 240  
 Pro Phe His Val Met Leu Leu Ile Arg Cys Ile Leu Glu His Ala Val  
 245 250 255  
 5 Asn Phe Glu Asp His Ser Asn Ser Gly Lys Arg Thr Tyr Thr Met Tyr  
 260 265 270  
 Arg Ile Thr Val Ala Leu Thr Ser Leu Asn Cys Val Ala Asp Pro Ile  
 275 280 285  
 10 Leu Tyr Cys Phe Val Thr Glu Thr Gly Arg Tyr Asp Met Trp Asn Ile  
 290 295 300  
 Leu Lys Phe Cys Thr Gly Arg Cys Asn Thr Ser Gln Arg Gln Arg Lys  
 305 310 315 320  
 Arg Ile Leu Ser Val Ser Thr Lys Asp Thr Met Glu Leu Glu Val Leu  
 325 330 335  
 15 Glu

(136) INFORMATION FOR SEQ ID NO:135:

(i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 999 base pairs  
 20 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:135:

25 ATGGTGAAC CCACCCACCG TGGGATGCAC ACTTCTCTGC ACCTCTGGAA CCGCAGCAGT  
 60  
 TACAGACTGC ACAGCAATGC CAGTGAGTCC CTTGGAAAAG GCTACTCTGA TGGAGGGTGC  
 120  
 TACGAGCAAC TTTTGTCTC TCCTGAGGTG TTTGTGACTC TGGGTGTCAT CAGCTTGTG  
 30 180  
 GAGAATATCT TAGTGATTGT GGCAATAGCC AAGAACAAGA ATCTGCATTC ACCCATGTAC  
 240  
 TTTTTCATCT GCAGCTTGGC TGTGGCTGAT ATGCTGGTGA GCGTTTCAA TGGATCAGAA  
 300  
 35 ACCATTATCA TCACCCTATT AAACAGTACA GATACGGATG CACAGAGTTT CACAGTGAAT  
 360

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ATTGATAATG TCATTGACTC GGTGATCTGT AGCTCCTTGC TTGCATCCAT TTGCAGCCTG  
420

CTTTCAATTG CAGTGGACAG GTACTTTACT ATCTTCTATG CTCTCCAGTA CCATAACATT  
480

5 ATGACAGTTA AGCGGGTTGG GATCAGCATA AGTTGTATCT GGGCAGCTTG CACGGTTTCA  
540

GGCATTTTGT TCATCATTTA CTCAGATAGT AGTGCTGTCA TCATCTGCCT CATCACCATG  
600

10 TTCTTCACCA TGCTGGCTCT CATGGCTTCT CTCTATGTCC ACATGTTCCCT GATGGCCAGG  
660

CTTCACATTA AGAGGATTGC TGTCTCCCC GGCCTGGTG CCATCCGCCA AGGTGCCAAT  
720

ATGAAGGGAA AAATTACCTT GACCATCCTG ATTGGCGTCT TTGTTGTCTG CTGGGCCCCA  
780

15 TTCTTCCTCC ACTTAATATT CTACATCTCT TGTCTCAGA ATCCATATTG TGTGTGCTTC  
840

ATGTCTCACT TTAACCTGTA TCTCATACTG ATCATGTGTA ATTCAATCAT CGATCCTCTG  
900

20 ATTTATGCAC TCCGGAGTCA AGAACTGAGG AAAACCTTCA AAGAGATCAT CTGTTGCTAT  
960

CCCCTGGGAG GCCTTTGTGA CTTGTCTAGC AGATATTAA  
999

(137) INFORMATION FOR SEQ ID NO:136:

- 25 (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 332 amino acids  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS:  
 (D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein

30 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:136:

Met Val Asn Ser Thr His Arg Gly Met His Thr Ser Leu His Leu Trp  
1 5 10 15

Asn Arg Ser Ser Tyr Arg Leu His Ser Asn Ala Ser Glu Ser Leu Gly  
20 25 30

35 Lys Gly Tyr Ser Asp Gly Gly Cys Tyr Glu Gln Leu Phe Val Ser Pro  
35 40 45

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	Glu Val Phe Val Thr Leu Gly Val Ile Ser Leu Leu Glu Asn Ile Leu	
	50	55 60
	Val Ile Val Ala Ile Ala Lys Asn Lys Asn Leu His Ser Pro Met Tyr	
	65	70 75 80
5	Phe Phe Ile Cys Ser Leu Ala Val Ala Asp Met Leu Val Ser Val Ser	
		85 90 95
	Asn Gly Ser Glu Thr Ile Ile Ile Thr Leu Leu Asn Ser Thr Asp Thr	
		100 105 110
10	Asp Ala Gln Ser Phe Thr Val Asn Ile Asp Asn Val Ile Asp Ser Val	
		115 120 125
	Ile Cys Ser Ser Leu Leu Ala Ser Ile Cys Ser Leu Leu Ser Ile Ala	
		130 135 140
	Val Asp Arg Tyr Phe Thr Ile Phe Tyr Ala Leu Gln Tyr His Asn Ile	
	145	150 155 160
15	Met Thr Val Lys Arg Val Gly Ile Ser Ile Ser Cys Ile Trp Ala Ala	
		165 170 175
	Cys Thr Val Ser Gly Ile Leu Phe Ile Ile Tyr Ser Asp Ser Ser Ala	
		180 185 190
20	Val Ile Ile Cys Leu Ile Thr Met Phe Phe Thr Met Leu Ala Leu Met	
		195 200 205
	Ala Ser Leu Tyr Val His Met Phe Leu Met Ala Arg Leu His Ile Lys	
		210 215 220
	Arg Ile Ala Val Leu Pro Gly Thr Gly Ala Ile Arg Gln Gly Ala Asn	
	225	230 235 240
25	Met Lys Gly Lys Ile Thr Leu Thr Ile Leu Ile Gly Val Phe Val Val	
		245 250 255
	Cys Trp Ala Pro Phe Phe Leu His Leu Ile Phe Tyr Ile Ser Cys Pro	
		260 265 270
30	Gln Asn Pro Tyr Cys Val Cys Phe Met Ser His Phe Asn Leu Tyr Leu	
		275 280 285
	Ile Leu Ile Met Cys Asn Ser Ile Ile Asp Pro Leu Ile Tyr Ala Leu	
		290 295 300
	Arg Ser Gln Glu Leu Arg Lys Thr Phe Lys Glu Ile Ile Cys Cys Tyr	
	305	310 315 320
35	Pro Leu Gly Gly Leu Cys Asp Leu Ser Ser Arg Tyr	
		325 330

(138) INFORMATION FOR SEQ ID NO:137:

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- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 33 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

5

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:137:

GCCAATATGA AGGGAAAAAT TACCTTGACC ATC  
33

10 (137) INFORMATION FOR SEQ ID NO:138:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 31 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

15

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:138:

CTCCTTCGGT CCTCCTATCG TTGTCAGAAG T  
31

20 (140) INFORMATION FOR SEQ ID NO:139:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 1842 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

25

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:139:

ATGGGGCCCA CCCTAGCGGT TCCCACCCCC TATGGCTGTA TTGGCTGTAA GCTACCCCAG 60  
CCAGAATACC CACCGGCTCT AATCATCTTT ATGTTCTGCG CGATGGTTAT CACCATCGTT 120  
30 GTAGACCTAA TCGGCAACTC CATGGTCATT TTGGCTGTGA CGAAGAACAA GAAGCTCCGG 180  
AATTCTGGCA ACATCTTCGT GGTCACTCTC TCTGTGGCCG ATATGCTGGT GGCCATCTAC 240  
CCATACCCTT TGATGCTGCA TGCCATGTCC ATTGGGGGCT GGGATCTGAG CCAGTTACAG 300  
TGCCAGATGG TCGGGTTCAT CACAGGGCTG AGTGTGGTCG GCTCCATCTT CAACATCGTG 360



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GCAATCGCTA TCAACCGTTA CTGCTACATC TGCCACAGCC TCCAGTACGA ACGGATCTTC 420  
AGTGTGCGCA ATACCTGCAT CTACCTGGTC ATCACCTGGA TCATGACCGT CCTGGCTGTC 480  
CTGCCCCAACA TGTACATTGG CACCATCGAG TACGATCCTC GCACCTACAC CTGCATCTTC 540  
AACTATCTGA ACAACCCTGT CTTCACTGTT ACCATCGTCT GCATCCACTT CGTCTCCCT 600  
5 CTCTCATCG TGGGTTTCTG CTACGTGAGG ATCTGGACCA AAGTGCTGGC GGCCCCGTGAC 660  
CCTGCAGGGC AGAATCCTGA CAACCAACTT GCTGAGGTTT GCAATTTTCT AACCATGTTT 720  
GTGATCTTCC TCCTCTTTGC AGTGTGCTGG TGCCCTATCA ACGTGCTCAC TGTCTTGGTG 780  
GCTGTCACTC CGAAGGAGAT GGCAGGCAAG ATCCCCAACT GGCTTTATCT TGCAGCCTAC 840  
TTCATAGCCT ACTTCAACAG CTGCCTCAAC GCTGTGATCT ACGGGCTCCT CAATGAGAAT 900  
10 TTCCGAAGAG AATACTGGAC CATCTTCCAT GCTATGCGGC ACCCTATCAT ATTCTTCCCT 960  
GGCCTCATCA GTGATATTCG TGAGATGCAG GAGGCCCCGT CCCTGGCCCCG CGCCCGTGCC 1020  
CATGCTCGCG ACCAAGCTCG TGAACAAGAC CGTGCCCATG CCTGTCCTGC TGTGGAGGAA 1080  
ACCCCGATGA ATGTCCGGAA TGTTCATTA CCTGGTGATG CTGCAGCTGG CCACCCGAC 1140  
CGTGCTCTG GCCACCCTAA GCCCCATTCC AGATCCTCCT CTGCCTATCG CAAATCTGCC 1200  
15 TCTACCCACC ACAAGTCTGT CTTTAGCCAC TCCAAGGCTG CCTCTGGTCA CCTCAAGCCT 1260  
GTCTCTGGCC ACTCCAAGCC TGCTCTGGT CACCCCAAGT CTGCCACTGT CTACCCTAAG 1320  
CCTGCCTCTG TCCATTTCOA GGGTGACTCT GTCCATTTC AAGGTGACTC TGTCCATTTC 1380  
AAGCCTGACT CTGTTCAATT CAAGCCTGCT TCCAGCAACC CCAAGCCCAT CACTGGCCAC 1440  
CATGTCTCTG CTGGCAGCCA CTCCAAGTCT GCCTTCAGTG CTGCCACCAG CCACCCTAAA 1500  
20 CCCATCAAGC CAGCTACCAG CCATGCTGAG CCCACCACTG CTGACTATCC CAAGCCTGCC 1560  
ACTACCAGCC ACCCTAAGCC CGCTGCTGCT GACAACCCTG AGCTCTCTGC CTCCCATTGC 1620  
CCCGAGATCC CTGCCATTGC CCACCCTGTG TCTGACGACA GTGACCTCCC TGAGTCGGCC 1680  
TCTAGCCCTG CCGCTGGGCC CACCAAGCCT GCTGCCAGCC AGCTGGAGTC TGACACCATC 1740  
GCTGACCTTC CTGACCCTAC TGTAGTCACT ACCAGTACCA ATGATTACCA TGATGTCGTG 1800  
25 GTTGTGATG TTGAAGATGA TCCTGATGAA ATGGCTGTGT GA 1842

(141) INFORMATION FOR SEQ ID NO:140:

## (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 613 amino acids

(B) TYPE: amino acid

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(C) STRANDEDNESS:

(D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:140:

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5   Met Gly Pro Thr Leu Ala Val Pro Thr Pro Tyr Gly Cys Ile Gly Cys
    1             5             10             15

    Lys Leu Pro Gln Pro Glu Tyr Pro Pro Ala Leu Ile Ile Phe Met Phe
      20             25             30

    Cys Ala Met Val Ile Thr Ile Val Val Asp Leu Ile Gly Asn Ser Met
10   35             40             45

    Val Ile Leu Ala Val Thr Lys Asn Lys Lys Leu Arg Asn Ser Gly Asn
      50             55             60

    Ile Phe Val Val Ser Leu Ser Val Ala Asp Met Leu Val Ala Ile Tyr
    65             70             75             80

15   Pro Tyr Pro Leu Met Leu His Ala Met Ser Ile Gly Gly Trp Asp Leu
      85             90             95

    Ser Gln Leu Gln Cys Gln Met Val Gly Phe Ile Thr Gly Leu Ser Val
      100            105            110

20   Val Gly Ser Ile Phe Asn Ile Val Ala Ile Ala Ile Asn Arg Tyr Cys
      115            120            125

    Tyr Ile Cys His Ser Leu Gln Tyr Glu Arg Ile Phe Ser Val Arg Asn
      130            135            140

    Thr Cys Ile Tyr Leu Val Ile Thr Trp Ile Met Thr Val Leu Ala Val
      145            150            155            160

25   Leu Pro Asn Met Tyr Ile Gly Thr Ile Glu Tyr Asp Pro Arg Thr Tyr
      165            170            175

    Thr Cys Ile Phe Asn Tyr Leu Asn Asn Pro Val Phe Thr Val Thr Ile
      180            185            190

    Val Cys Ile His Phe Val Leu Pro Leu Leu Ile Val Gly Phe Cys Tyr
30   195            200            205

    Val Arg Ile Trp Thr Lys Val Leu Ala Ala Arg Asp Pro Ala Gly Gln
      210            215            220

    Asn Pro Asp Asn Gln Leu Ala Glu Val Arg Asn Phe Leu Thr Met Phe
      225            230            235            240

35   Val Ile Phe Leu Leu Phe Ala Val Cys Trp Cys Pro Ile Asn Val Leu
      245            250            255

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Thr Val Leu Val Ala Val Ser Pro Lys Glu Met Ala Gly Lys Ile Pro  
 260 265 270  
 Asn Trp Leu Tyr Leu Ala Ala Tyr Phe Ile Ala Tyr Phe Asn Ser Cys  
 275 280 285  
 5 Leu Asn Ala Val Ile Tyr Gly Leu Leu Asn Glu Asn Phe Arg Arg Glu  
 290 295 300  
 Tyr Trp Thr Ile Phe His Ala Met Arg His Pro Ile Ile Phe Phe Pro  
 305 310 315 320  
 10 Gly Leu Ile Ser Asp Ile Arg Glu Met Gln Glu Ala Arg Thr Leu Ala  
 325 330 335  
 Arg Ala Arg Ala His Ala Arg Asp Gln Ala Arg Glu Gln Asp Arg Ala  
 340 345 350  
 His Ala Cys Pro Ala Val Glu Glu Thr Pro Met Asn Val Arg Asn Val  
 355 360 365  
 15 Pro Leu Pro Gly Asp Ala Ala Ala Gly His Pro Asp Arg Ala Ser Gly  
 370 375 380  
 His Pro Lys Pro His Ser Arg Ser Ser Ser Ala Tyr Arg Lys Ser Ala  
 385 390 395 400  
 20 Ser Thr His His Lys Ser Val Phe Ser His Ser Lys Ala Ala Ser Gly  
 405 410 415  
 His Leu Lys Pro Val Ser Gly His Ser Lys Pro Ala Ser Gly His Pro  
 420 425 430  
 Lys Ser Ala Thr Val Tyr Pro Lys Pro Ala Ser Val His Phe Lys Gly  
 435 440 445  
 25 Asp Ser Val His Phe Lys Gly Asp Ser Val His Phe Lys Pro Asp Ser  
 450 455 460  
 Val His Phe Lys Pro Ala Ser Ser Asn Pro Lys Pro Ile Thr Gly His  
 465 470 475 480  
 30 His Val Ser Ala Gly Ser His Ser Lys Ser Ala Phe Ser Ala Ala Thr  
 485 490 495  
 Ser His Pro Lys Pro Ile Lys Pro Ala Thr Ser His Ala Glu Pro Thr  
 500 505 510  
 Thr Ala Asp Tyr Pro Lys Pro Ala Thr Thr Ser His Pro Lys Pro Ala  
 515 520 525  
 35 Ala Ala Asp Asn Pro Glu Leu Ser Ala Ser His Cys Pro Glu Ile Pro  
 530 535 540  
 Ala Ile Ala His Pro Val Ser Asp Asp Ser Asp Leu Pro Glu Ser Ala

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545                                      550                                      555                                      560

Ser Ser Pro Ala Ala Gly Pro Thr Lys Pro Ala Ala Ser Gln Leu Glu  
565                                      570                                      575

Ser Asp Thr Ile Ala Asp Leu Pro Asp Pro Thr Val Val Thr Thr Ser  
580                                      585                                      590

Thr Asn Asp Tyr His Asp Val Val Val Asp Val Glu Asp Asp Pro  
595                                      600                                      605

Asp Glu Met Ala Val  
610

10 (142) INFORMATION FOR SEQ ID NO:141:

(i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 1842 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 15 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:141:

ATGGGGCCCA CCCTAGCGGT TCCCACCCCC TATGGCTGTA TTGGCTGTAA GCTACCCAG 60

CCAGAATACC CACCGGCTCT AATCATCTTT ATGTTCTGCG CGATGGTTAT CACCATCGTT 120

20 GTAGACCTAA TCGGCAACTC CATGGTCATT TTGGCTGTGA CGAAGAACAA GAAGCTCCGG 180

AATTCTGGCA ACATCTTCGT GGTCACTCTC TCTGTGGCCG ATATGCTGGT GGCCATCTAC 240

CCATACCCTT TGATGCTGCA TGCCATGTCC ATTGGGGGCT GGGATCTGAG CCAGTTACAG 300

TGCCAGATGG TCGGGTTCAT CACAGGGCTG AGTGTGGTCG GCTCCATCTT CAACATCGTG 360

GCAATCGCTA TCAACCGTTA CTGCTACATC TGCCACAGCC TCCAGTACGA ACGGATCTTC 420

25 AGTGTGCGCA ATACCTGCAT CTACCTGGTC ATCACCTGGA TCATGACCGT CCTGGCTGTC 480

CTGCCCCACA TGTACATTGG CACCATCGAG TACGATCCTC GCACCTACAC CTGCATCTTC 540

AACATCTGA ACAACCCTGT CTTCACTGTT ACCATCGTCT GCATCCACTT CGTCTCCCT 600

CTCCTCATCG TGGGTTTCTG CTACGTGAGG ATCTGGACCA AAGTGCTGGC GGCCCGTGAC 660

CCTGCAGGGC AGAATCCTGA CAACCAACTT GCTGAGGTTC GCAATAAACT AACCATGTTT 720

30 GTGATCTTCC TCCTCTTTGC AGTGTGCTGG TGCCCTATCA ACGTGCTCAC TGTCTTGGTG 780

GCTGTCACTC CGAAGGAGAT GGCAGGCAAG ATCCCCAACT GGCTTTATCT TGCAGCCTAC 840

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TTCATAGCCT ACTTCAACAG CTGCCTCAAC GCTGTGATCT ACGGGCTCCT CAATGAGAAT 900  
 TTCCGAAGAG AATACTGGAC CATCTTCCAT GCTATGCGGC ACCCTATCAT ATTCTTCTCT 960  
 GGCCTCATCA GTGATATTCG TGAGATGCAG GAGGCCCCGTA CCCTGGCCCCG CGCCCGTGCC 1020  
 CATGCTCGCG ACCAAGCTCG TGAACAAGAC CGTGCCCATG CCTGTCCTGC TGTGGAGGAA 1080  
 5 ACCCCGATGA ATGTCCGGA TGTTCATTA CCTGGTGATG CTGCAGCTGG CCACCCCGAC 1140  
 CGTGCTCTG GCCACCCTAA GCCCCATTCC AGATCCTCCT CTGCCTATCG CAAATCTGCC 1200  
 TCTACCCACC ACAAGTCTGT CTTTAGCCAC TCCAAGGCTG CCTCTGGTCA CCTCAAGCCT 1260  
 GTCTCTGGCC ACTCCAAGCC TGCCTCTGGT CACCCCAAGT CTGCCACTGT CTACCCTAAG 1320  
 CCTGCCTCTG TCCATTTCAA GGCTGACTCT GTCCATTTC AAGGTGACTC TGTCCATTTC 1380  
 10 AAGCCTGACT CTGTTCAATT CAAGCCTGCT TCCAGCAACC CCAAGCCCAT CACTGGCCAC 1440  
 CATGTCTCTG CTGGCAGCCA CTCCAAGTCT GCCTTCAATG CTGCCACCAG CCACCCTAAA 1500  
 CCCATCAAGC CAGCTACCAG CCATGCTGAG CCCACCACTG CTGACTATCC CAAGCCTGCC 1560  
 ACTACCAGCC ACCCTAAGCC CGCTGCTGCT GACAACCCTG AGCTCTCTGC CTCCCATTGC 1620  
 CCCGAGATCC CTGCCATTGC CCACCCTGTG TCTGACGACA GTGACCTCCC TGAGTCGGCC 1680  
 15 TCTAGCCCTG CCGCTGGGCC CACCAAGCCT GCTGCCAGCC AGCTGGAGTC TGACACCATC 1740  
 GCTGACCTTC CTGACCCTAC TGTAGTCACT ACCAGTACCA ATGATTACCA TGATGTCGTG 1800  
 GTTGTGATG TTGAAGATGA TCCTGATGAA ATGGCTGTGT GA 1842

(143) INFORMATION FOR SEQ ID NO:142:

- 20 (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 613 amino acids  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS:  
 (D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein

- 25 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:142:

Met Gly Pro Thr Leu Ala Val Pro Thr Pro Tyr Gly Cys Ile Gly Cys  
 1 5 10 15

Lys Leu Pro Gln Pro Glu Tyr Pro Pro Ala Leu Ile Ile Phe Met Phe  
 20 25 30

30 Cys Ala Met Val Ile Thr Ile Val Val Asp Leu Ile Gly Asn Ser Met  
 35 40 45

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	Val	Ile	Leu	Ala	Val	Thr	Lys	Asn	Lys	Lys	Leu	Arg	Asn	Ser	Gly	Asn	
	50						55					60					
	Ile	Phe	Val	Val	Ser	Leu	Ser	Val	Ala	Asp	Met	Leu	Val	Ala	Ile	Tyr	
	65					70					75					80	
5	Pro	Tyr	Pro	Leu	Met	Leu	His	Ala	Met	Ser	Ile	Gly	Gly	Trp	Asp	Leu	
					85					90					95		
	Ser	Gln	Leu	Gln	Cys	Gln	Met	Val	Gly	Phe	Ile	Thr	Gly	Leu	Ser	Val	
				100					105					110			
10	Val	Gly	Ser	Ile	Phe	Asn	Ile	Val	Ala	Ile	Ala	Ile	Asn	Arg	Tyr	Cys	
			115					120					125				
	Tyr	Ile	Cys	His	Ser	Leu	Gln	Tyr	Glu	Arg	Ile	Phe	Ser	Val	Arg	Asn	
	130						135					140					
	Thr	Cys	Ile	Tyr	Leu	Val	Ile	Thr	Trp	Ile	Met	Thr	Val	Leu	Ala	Val	
	145					150					155					160	
15	Leu	Pro	Asn	Met	Tyr	Ile	Gly	Thr	Ile	Glu	Tyr	Asp	Pro	Arg	Thr	Tyr	
				165						170					175		
	Thr	Cys	Ile	Phe	Asn	Tyr	Leu	Asn	Asn	Pro	Val	Phe	Thr	Val	Thr	Ile	
				180					185					190			
20	Val	Cys	Ile	His	Phe	Val	Leu	Pro	Leu	Leu	Ile	Val	Gly	Phe	Cys	Tyr	
		195						200					205				
	Val	Arg	Ile	Trp	Thr	Lys	Val	Leu	Ala	Ala	Arg	Asp	Pro	Ala	Gly	Gln	
		210					215					220					
	Asn	Pro	Asp	Asn	Gln	Leu	Ala	Glu	Val	Arg	Asn	Lys	Leu	Thr	Met	Phe	
	225				230						235					240	
25	Val	Ile	Phe	Leu	Leu	Phe	Ala	Val	Cys	Trp	Cys	Pro	Ile	Asn	Val	Leu	
				245						250					255		
	Thr	Val	Leu	Val	Ala	Val	Ser	Pro	Lys	Glu	Met	Ala	Gly	Lys	Ile	Pro	
			260						265					270			
30	Asn	Trp	Leu	Tyr	Leu	Ala	Ala	Tyr	Phe	Ile	Ala	Tyr	Phe	Asn	Ser	Cys	
		275						280					285				
	Leu	Asn	Ala	Val	Ile	Tyr	Gly	Leu	Leu	Asn	Glu	Asn	Phe	Arg	Arg	Glu	
		290					295					300					
	Tyr	Trp	Thr	Ile	Phe	His	Ala	Met	Arg	His	Pro	Ile	Ile	Phe	Phe	Ser	
	305					310					315					320	
35	Gly	Leu	Ile	Ser	Asp	Ile	Arg	Glu	Met	Gln	Glu	Ala	Arg	Thr	Leu	Ala	
				325						330					335		
	Arg	Ala	Arg	Ala	His	Ala	Arg	Asp	Gln	Ala	Arg	Glu	Gln	Asp	Arg	Ala	

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	340	345	350
	His Ala Cys Pro Ala Val Glu Glu Thr Pro Met Asn Val Arg Asn Val		
	355	360	365
5	Pro Leu Pro Gly Asp Ala Ala Ala Gly His Pro Asp Arg Ala Ser Gly		
	370	375	380
	His Pro Lys Pro His Ser Arg Ser Ser Ser Ala Tyr Arg Lys Ser Ala		
	385	390	395 400
	Ser Thr His His Lys Ser Val Phe Ser His Ser Lys Ala Ala Ser Gly		
	405	410	415
10	His Leu Lys Pro Val Ser Gly His Ser Lys Pro Ala Ser Gly His Pro		
	420	425	430
	Lys Ser Ala Thr Val Tyr Pro Lys Pro Ala Ser Val His Phe Lys Ala		
	435	440	445
15	Asp Ser Val His Phe Lys Gly Asp Ser Val His Phe Lys Pro Asp Ser		
	450	455	460
	Val His Phe Lys Pro Ala Ser Ser Asn Pro Lys Pro Ile Thr Gly His		
	465	470	475 480
	His Val Ser Ala Gly Ser His Ser Lys Ser Ala Phe Asn Ala Ala Thr		
	485	490	495
20	Ser His Pro Lys Pro Ile Lys Pro Ala Thr Ser His Ala Glu Pro Thr		
	500	505	510
	Thr Ala Asp Tyr Pro Lys Pro Ala Thr Thr Ser His Pro Lys Pro Ala		
	515	520	525
25	Ala Ala Asp Asn Pro Glu Leu Ser Ala Ser His Cys Pro Glu Ile Pro		
	530	535	540
	Ala Ile Ala His Pro Val Ser Asp Asp Ser Asp Leu Pro Glu Ser Ala		
	545	550	555 560
	Ser Ser Pro Ala Ala Gly Pro Thr Lys Pro Ala Ala Ser Gln Leu Glu		
	565	570	575
30	Ser Asp Thr Ile Ala Asp Leu Pro Asp Pro Thr Val Val Thr Thr Ser		
	580	585	590
	Thr Asn Asp Tyr His Asp Val Val Val Val Asp Val Glu Asp Asp Pro		
	595	600	605
35	Asp Glu Met Ala Val		
	610		

(144) INFORMATION FOR SEQ ID NO:143:

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- (i) SEQUENCE CHARACTERISTICS:  
    (A) LENGTH: 33 base pairs  
    (B) TYPE: nucleic acid  
    (C) STRANDEDNESS: single  
5     (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:143:

GCTGAGGTTC GCAATAAACT AACCATGTTT GTG

33

(145) INFORMATION FOR SEQ ID NO:144:

- 10     (i) SEQUENCE CHARACTERISTICS:  
        (A) LENGTH: 30 base pairs  
        (B) TYPE: nucleic acid  
        (C) STRANDEDNESS: single  
        (D) TOPOLOGY: linear

15     (ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:144:

CTCCTTCGGT CCTCCTATCG TTGTCAGAAG T

31

(146) INFORMATION FOR SEQ ID NO:145:

- 20     (i) SEQUENCE CHARACTERISTICS:  
        (A) LENGTH: 27 base pairs  
        (B) TYPE: nucleic acid  
        (C) STRANDEDNESS: single  
        (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

25     (iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:145:

TTAGATATCG GGGCCCACCC TAGCGGT

33

(147) INFORMATION FOR SEQ ID NO:146:

- 30     (i) SEQUENCE CHARACTERISTICS:  
        (A) LENGTH: 29 base pairs  
        (B) TYPE: nucleic acid  
        (C) STRANDEDNESS: single  
        (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)



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(iv) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:146:

GGTACCCCCA CAGCCATTTC ATCAGGATC

33